

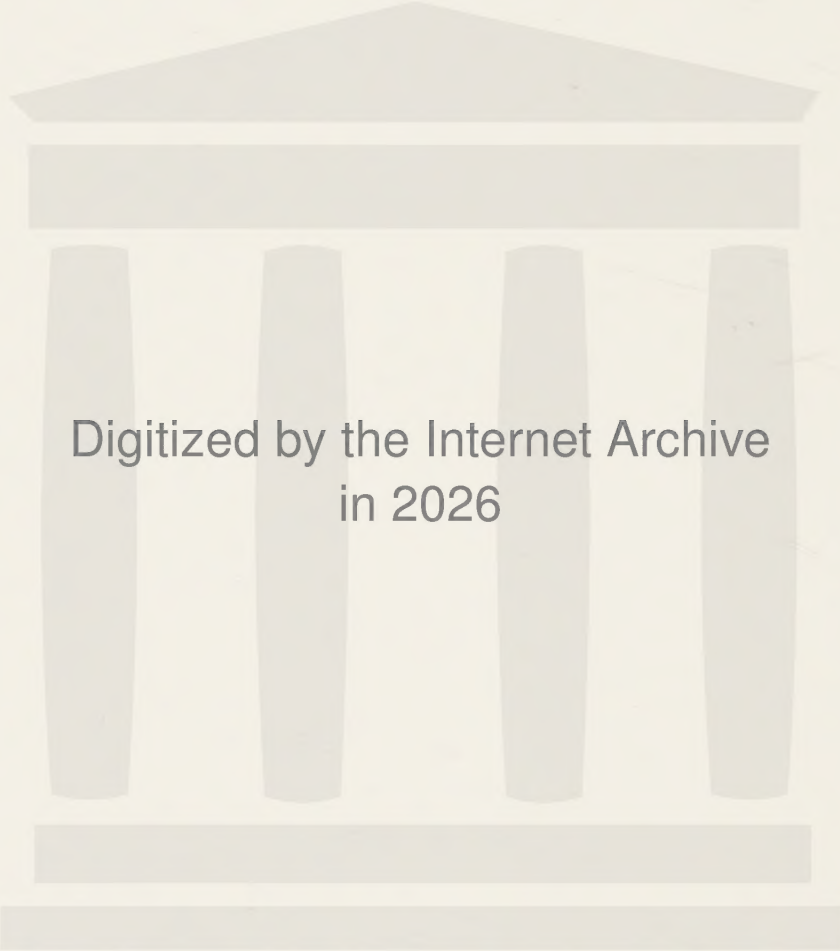
Lund 1983.

Svend Borup Christensen

*A CLINICAL EPIDEMIOLOGICAL STUDY
OF THYROID CARCINOMA
IN MALMÖ, SWEDEN*



Malmö 1983



Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41546725_0048

A CLINICAL EPIDEMIOLOGICAL STUDY OF THYROID
CARCINOMA IN MALMÖ, SWEDEN

AKADEMISK AVHANDLING

som med vederbörligt tillstånd av Medicinska Fakulteten vid
Lunds Universitet för avläggande av doktorsexamen i medicinsk
vetenskap kommer att offentligen försvaras i Medicinska
klinikens aula, Allmänna sjukhuset i Malmö, fredagen den
3 juni 1983 kl 09.15

av

Svend Borup Christensen
leg läk, Mlm

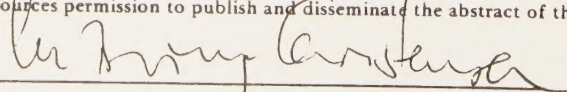
Organization LUND UNIVERSITY Departments of Surgery, Preventive Medicine and Pathology Malmö General Hospital S-214 01 Malmö, Sweden		Document name DOCTORAL DISSERTATION	
		Date of issue 1983-06-03	
		CODEN: LUMEDW/(MESM-1011)/1-77(1983)	
Author(s) Svend Borup Christensen		Sponsoring organization	
Title and subtitle A clinical epidemiological study of thyroid carcinoma in Malmö, Sweden.			
Abstract Incidence, mortality rate, clinical symptoms and signs, results of surgical treatment and the significance of various prognostic factors in thyroid carcinoma (TC) were estimated by studying all patients with clinical TC (n=104) and all cases of fatal TC (n=38) in Malmö 1960-1977. The average annual incidence per 100,000 was 2.4, the corresponding mortality rate 0.9. An increase in incidence during the later part of the study was suggested to be caused by improved medical care since only the number of tumors with less advanced growth increased. A solitary thyroid nodule was the only sign in 60% of the patients with clinical TC. The prevalence of this sign was estimated in a population survey of 477 middle-aged women, and was found to be 6.5%. The usefulness of various diagnostic procedures was evaluated, both among patients with known TC and among the middle-aged women, as well as in a special series of 100 patients surgically treated for a solitary nodule. Fine-needle aspiration cytology was considered the best single method in the management of patients with a solitary nodule, but also physical examination, thyroid scan, and, to some extent, serum thyroglobulin were found to be of value. Ninety of the 104 patients were surgically treated. Of these, 78 were considered to be operated for cure, 52 by a procedure less than total thyroidectomy. No patient operated for cure died from TC, and only one had a local recurrence which was treated successfully. A thyroid lobectomy was considered a sufficient surgical procedure in most cases of localized TC. The percentage distribution by histologic type of the 104 TC:s clinically diagnosed was: papillary cancer 65%, follicular 21%, medullary 4%, and anaplastic 12%. The prognosis was best for patients with papillary TC, worst for those with anaplastic TC. Age was found to be an important prognostic predictor: deaths from TC diagnosed before the age of 60 were infrequent, whereas the disease after this age increasingly often was fatal.			
Key words Thyroid carcinoma, prevalence, incidence, mortality rate, solitary thyroid nodule, conservative surgical approach			
Classification system and/or index terms (if any)			
Supplementary bibliographical information		Language English	
ISSN and key title		ISBN	
Recipient's notes	Number of pages 77		Price
	Security classification		

Distribution by (name and address)

Svend Borup Christensen, Department of Surgery,
Malmö General Hospital, S-214 01 Malmö, Sweden

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature



Date 1983 03 29

From the Department of Surgery, the Department of Preventive Medicine, the Department of Nuclear Medicine, the Department of Cytology and the Department of Pathology, University of Lund, Malmö, General Hospital, Malmö Sweden.

A clinical epidemiological study of thyroid carcinoma in Malmö, Sweden

Svend Borup Christensen

Malmö 1983

Acknowledgements

I am sincerely indebted to

Bengt Zederfeldt, my chief, for his generous support and constructive criticism, particularly during the last year of the study,

my co-workers, in particular *Sten Tibblin* for initiating this study, *Otto Ljungberg* for careful professional work, and both for wise guidance and criticism,

Lars Janson, Medicinsk & Teknisk Ritstjänst, for skilful drawings,

Mona Stewenius for revising the English text,

Ingrid Malmqvist and her colleagues at the Department of Preventive Medicine for valuable help with the prevalence study (I),

Eva Prahl for performing the extensive secretarial work in a skilful and devoted way.



The present dissertation is based on the following papers:

- I THE PREVALENCE OF THYROID DISORDERS IN A MIDDLE-AGED FEMALE POPULATION,
WITH SPECIAL REFERENCE TO THE SOLITARY THYROID NODULE
Svend Borup Christensen, Ulla-Britt Ericsson, Lars Janzon,
Sten Tibblin & Erik Trel
Acta Chir Scand. Submitted for publication.

- II PREDICTION OF MALIGNANCY IN SOLITARY THYROID NODULES BY PHYSICAL
EXAMINATION, THYROID SCAN, ASPIRATION BIOPSY CYTOLOGY AND SERUM
THYROGLOBULIN. A PROSPECTIVE STUDY OF 100 PATIENTS, SURGICALLY TREATED.
Svend Borup Christensen, Lennart Bondeson, Ulla-Britt Ericsson &
Karin Lindholm
Submitted for publication.

- III THYROID CARCINOMA IN MALMÖ 1960-1977. EPIDEMIOLOGICAL, CLINICAL AND
PROGNOSTIC FINDINGS IN A DEFINED URBAN POPULATION
Svend Borup Christensen, Otto Ljungberg & Sten Tibblin
Cancer. In press.

- IV SURGICAL TREATMENT OF THYROID CARCINOMA IN A DEFINED POPULATION
1960-1977. EVALUATION OF THE RESULTS AFTER A CONSERVATIVE SURGICAL
APPROACH
Svend Borup Christensen, Otto Ljungberg & Sten Tibblin
Am J Surg. In press.

- V MORTALITY FROM THYROID CARCINOMA IN A DEFINED POPULATION 1960-1977.
A CLINICAL AND PATHOLOGICAL STUDY OF 38 FATAL CASES.
Svend Borup Christensen & Otto Ljungberg
Cancer. Submitted for publication.

These papers will be referred to in the text by their Roman numerals I - V.

Contents

ABBREVIATIONS AND DEFINITIONS	6
INTRODUCTION AND PURPOSE	9
MATERIAL AND METHODS	13
RESULTS AND COMMENTS	
A. <u>Epidemiological aspects</u>	
1. Prevalence of palpable thyroid disorders	20
2. Prevalence of thyroid carcinoma	21
3. Incidence and mortality rate of TC in Malmö	23
4. Frequency of TC in palpable solitary nodules	25
B. <u>Etiology and clinical evaluation</u>	
1. Familial disposition	27
2. Irradiation to the neck	28
3. Presenting symptoms	29
4. History and physical examination	30
5. Thyroid scan	31
6. Aspiration biopsy cytology	32
7. Serum thyroglobulin	35
C. <u>Histopathology</u>	37
D. <u>Treatment</u>	
1. Surgical treatment and additional therapy	44
2. Non-surgical treatment	50

E. Survival

1. Survival time in fatal cases	53
2. Survival for all patients with thyroid carcinoma	54
3. Survival by histologic type	56
4. Survival by tumor stage	58
5. Survival by node status	60
6. Survival by age	62
7. Survival by sex	64

GENERAL SUMMARY AND CONCLUSIONS	67
---------------------------------	----

REFERENCES	70
------------	----

ARTICLES I - V	
----------------	--

Abbreviations and definitions

TC: Thyroid carcinoma.

Goiter: An enlargement of the thyroid and/or a deviation of its form and consistency making parts of the gland or the whole gland visible or palpable.

Prevalence: The total number of cases of disease in existence at a certain time in a designated population.

Incidence: The number of new cases of a specific disease occurring during a certain period. In the present study the incidence was given per 100,000 persons and year.

Age-specific incidence: The incidence in a particular age-group.

Age-standardized incidence: The incidence adjusted for age to a standard population. In the present study the census of Sweden in 1970 was used as standard population.

Detection rate: The ratio between the number of cases of disease actually detected during a certain period of time (incidence) and the total number of cases of disease in existence (prevalence) in the same population.

Mortality rate, age-specific mortality rate and age-standardized mortality rate: Correspond to the definitions of incidence terms where the number of new cases of disease is replaced by the number of deaths from a specific disease.

Differentiated TC: Papillary, follicular, and medullary TC.

Clinical TC: TC histologically confirmed, diagnosed or suspected *intra vitam*.

Occult TC: A TC not more than 1.5 cm in its largest diameter.

Intrathyroidal carcinoma: A TC larger than 1.5 cm in its largest diameter, not breaking through the thyroid capsule.

Extrathyroidal carcinoma: A TC larger than 1.5 cm in its largest diameter and with evidence of penetration of the thyroid capsule.

The definitions of occult, intrathyroidal and extrathyroidal were used without regard to whether or not metastases were present.

Incidental histopathologic finding (in a thyroid gland): A histopathologic finding in a surgical specimen, the site of which not corresponds to the palpation finding (index nodule) leading to surgery.

Incidental clinical finding: A clinical finding (for instance thyroid nodule) detected incidentally at clinical screening or at clinical examination for another purpose (than thyroid disease).

Total thyroidectomy: An operation with the intension of excizing all thyroid tissue.

Partial thyroidectomy: A thyroid operation less than total thyroidectomy.

Lobectomy: An operation with the intension of excizing one thyroid lobe including isthmus.

A curative operation: An operation where the surgeon peroperatively estimated that all cancer tissue was removed.

A palliative operation: An operation during which the surgeon estimates that cancer tissue was left either locally or as metastases.

Introduction and purpose

Thyroid carcinoma is an uncommon disease with an annual incidence ranging from 0.3 to 10 per 100,000 persons according to official statistics (1). The good prognosis of the differentiated forms of TC is apparent from the fact that the reported mortality rate is considerably lower than the incidence, particularly for younger age groups (2,3). Thorough histopathologic *post mortem*-studies of the thyroid gland (4,5,6) as well as extensive population surveys (7) indicate that the prevalence of TC is considerably higher than would appear from the annual incidence figures. This should imply that the number of patients having a clinical diagnosis of TC is dependent on the frequency and quality of clinical examinations and health screening procedures as well as on the accuracy of the histopathologic examination of surgically excised thyroid glands.

A lump in the neck is often the first and only sign of TC. Many patients with thyroid nodules are referred for surgery because malignancy cannot be ruled out. To assess such nodules adequately, it is important to know the prevalence of thyroid lesions in an unselected population. This is particularly true for solitary nodules, in which the risk of malignancy is considered to be high (8, 9). Most previous studies on the prevalence of goiter have paid little attention to the various subgroups of the condition (10).

Due to the great discrepancy between the prevalence of benign thyroid nodules and palpable TC there is a need of inexpensive, simple and safe methods to identify correctly those nodules which have to be surgically excised because of malignancy. Various forms of thyroid scanning have been widely used, but the accuracy of these methods in diagnosing TC has been disappointing. Fine-needle aspiration cytology has been a well established method in Sweden for many years (11,12,13), and recent reports from other countries have confirmed the value of this method for the evaluation of thyroid nodules (14-17). Still, however, many benign nodules have to be excised in order to find the malignant thyroid tumors. Therefore, further attempts to refine the existing diagnostic methods and to introduce new ones are desirable.

One factor, which, together with the low incidence, makes studies of TC difficult to perform, is that TC in fact represents several histologic and biologic entities. During the last decade, TC has generally been divided into four main histologic groups: papillary, follicular, medullary, and anaplastic carcinoma (18,19,20), each one having particular histopathologic, clinical, and prognostic qualities. The "mixed papillo-follicular carcinoma", previously often classified as a group of its own, is now commonly included within the group of papillary carcinoma. Although some authors regard Askanazy cell carcinomas (also called Hürthle cell or oxyphil carcinomas) as a distinct group (21), these tumors have most often been included among the follicular carcinomas because the criteria for malignant diagnosis and the biologic behavior are similar (22,23). Tumors classified earlier as "small cell anaplastic carcinomas" seem to represent malignant lymphomas. It has been proposed that these tumors should be excluded from the group of anaplastic carcinoma thus leaving only carcinomas of the giant or spindle cell type as true members of the group (24).

Tumor stage, *i.e.* the anatomical extent of the malignant disease at diagnosis, has proven to be a most valuable prognostic predictor in many malignant diseases, including TC. For TC, however, no standardized staging classification system exists so far which has been practical and accepted internationally. Most commonly the thyroid tumors have been grouped as *occult, intrathyroidal, and extrathyroidal* (20,25) but also histopathologic findings such as vascular invasion and intrathyroidal dissemination of the tumor have been used as part of the basis for a division into stages (26, 27). Since the presence or absence of lymph node metastases seems to have little bearing on the prognosis (20,28), this is considered to be of limited value in the stage division. There has been most controversies regarding the occult carcinomas, which are commonly defined as thyroid tumors below 1.5 cm in size regardless of metastases. The conception of "occult carcinoma" was originally introduced to cover the small carcinomas, most often papillary in type which have been shown to occur in up to 28% of the thyroid glands in carefully performed autopsy studies (29). In recent years, however, reports have appeared on cases of occult carcinoma with poor prognosis (30,31), motivating a change in the definition of "occult".

Many accounts on prognostic factors in TC have been conflicting. This could be due to true differences between geographic areas, races, time periods or modes of treatment, but the explanation could also, in part, be methodological. Thus, patient materials may have been selected as to age and sex distribution (32) or selected because of accumulation of more advanced cases or cases with particular tumor types to certain centers (33). The method of tumor registration, *i.e.* compulsory or voluntary, may have a significance for the completeness and composition of the patient-materials collected from such registries. When patients are collected from more than one center or over a long period of time, several pathologists have usually been involved in the histopathologic diagnosis and classification. Histologic review of such materials may reduce the number of actual carcinomas and change the histologic distribution of the tumors (34).

The extent of surgical treatment of TC has long been a matter of dispute, mainly due to the lack of randomized trials. Particularly, there is disagreement whether cancer which is clinically confined to one lobe should be treated by total thyroidectomy (35,36) or by more conservative procedures (37,38). The most important argument for total thyroidectomy, at least in cases of papillary cancer, is the high frequency of microscopic cancer foci in the lobe opposite to the clinical cancer (39). The opponents to this idea claim that this phenomenon is of little clinical importance and that the complication rate following total thyroidectomy is not negligible.

The prognostic evaluation of TC requires a sufficiently long follow-up period. It has been claimed that deaths caused by TC occur 15-25 years after the primary treatment (37,40) and accordingly, follow-up periods of corresponding length have been recommended. However, the frequency of late deaths from TC is often uncertain, since autopsies have often not been performed to confirm TC as the cause of death. This is desirable, since deaths in patients having differentiated TC could be caused by metastases from other malignant tumors having been clinically unknown. Long follow-up periods result in very aged patient materials; such materials may have a deviating composition as to demographic, etiologic, histopathologic and clinical qualities. One way to estimate the

proportion of late deaths from TC, should be to study all fatal TC verified by autopsy in a defined area during a certain period of time.

In order to assess and generalize correctly such factors as incidence, mortality rate, clinical symptoms and signs, the benefit of various diagnostic procedures, age and sex distribution, effects of surgical treatment and prognosis in TC, some ideal conditions might be listed. Patient materials should be representative of a whole demographically defined population, the treatments given should be uniform and easy to classify, the follow-up should be complete, detailed and of sufficient length, all histopathologic material should be revised and reclassified to a current, generally accepted system and the autopsy frequency should be high. If these conditions could be to at least some extent fulfilled the possibility of comparing the findings in different areas and centers would improve.

The present study was undertaken with the following objectives:

- 1) to estimate the incidence and mortality rate of TC in a demographically well-defined area during a period of 18 years.
- 2) to estimate the prevalence of palpable thyroid disorders, particularly of a palpable solitary nodule, the most frequent sign of TC, in middle-aged women.
- 3) to evaluate the significance of anamnestic findings, physical examination, thyroid scan, fine-needle aspiration cytology, and serum thyroglobulin in the diagnosis of TC.
- 4) to evaluate the significance of the extent of the surgical treatment for the prognosis and postoperative complication rate.
- 5) to evaluate the significance of such factors as age, sex, histologic type and extension of tumor for the prognosis.
- 6) to estimate to what extent anaplastic carcinoma develop from differentiated forms of TC.
- 7) to determine the survival time for patients with the different histologic forms of TC in those cases the disease was fatal.

Material and methods

Malmö is an industrial coastal city in the southern part of Sweden. There were, on an average, 243,000 inhabitants during the years 1960-1977. The population is mainly urban but a minor part, living in the neighbouring districts, is originally rural. Goiter is considered non-endemic to the area (41). The average age distribution was very close to the distribution for the Swedish population as a whole during the corresponding period of time. The female part of the population was 51.8% compared with 50.3% for the whole nation. During the entire period the number of individuals 60 years of age or more increased by about 20,000 (58%), whereas changes in the other age groups generally followed changes in the total population.

There are three hospitals in the city, one general hospital, one mental hospital and one hospital for chronic diseases. All diagnostic procedures, treatment and follow-up of TC, were carried out in the general hospital. The surgery was almost exclusively carried out by senior surgeons with particular interest in thyroid surgery.

Autopsy was performed in 85.7% of all who died in Malmö 1960 to 1977. Sixty-eight per cent were clinical autopsies whereas 17.7% were medico-legal autopsies. In the clinical autopsies the thyroid gland was routinely examined and cut into slices 0.5 cm or less in thickness. Whenever suspicion of malignancy in thyroid nodules arose, a supplementary histologic examination was performed.

I. This study was a population survey performed during a seven-month period in 1979. 477 women, born in the years 1926 and 1931, participated in the study. These women were selected to represent the female population in Malmö, born in these years.

All women had a clinical examination by one and the same physician. Particular attention was paid to the presence or absence of goiter. The goiter was classified as diffuse enlargement, multiple nodules, or a solitary nodule.

All participants answered a questionnaire that included previous or current thyroid disease, signs of disturbance of the thyroid function, current medication, and family history of thyroid disease.

Before the clinical examination, a fasting blood sample was taken for the following tests: S-triiodothyronine (T_3), S-thyrotropin (TSH), S-thyroglobulin (Tg), and thyroglobulin antibodies. Radioimmunoassays were used to determine T_3 , TSH, and Tg (42,43).

All individuals who were found to have a goiter were offered a special examination comprising thyroid scintigraphy (using sodium pertechnetate Tc 99m) and fine-needle aspiration biopsy. Individuals who accepted this offer also underwent a clinical examination by another physician who decided on further treatment.

II. One hundred consecutive patients with a thyroid nodule, solitary by palpation, selected for surgical treatment at our department during a three-year period, were studied prospectively. Anamnestic data, findings at physical examination, results of thyroid scan and aspiration fine-needle biopsy, and preoperative serum thyroglobulin values were correlated to the histopathologic findings in the surgical specimens corresponding to the index nodule (table I). The cytologic as well as the histopathologic materials were reviewed and reclassified.

III. In this study the intention was to include those patients in Malmö in whom a diagnosis of TC was made or suggested *intra vitam* during the period 1960-1977. Altogether the diagnosis of TC was made in 210 individuals (fig 1). In 120 of these cases the histologic diagnosis was based on surgical specimens and in 90 on autopsy material. Sixty-two of the autopsy cases were considered "side findings" not related to the cause of

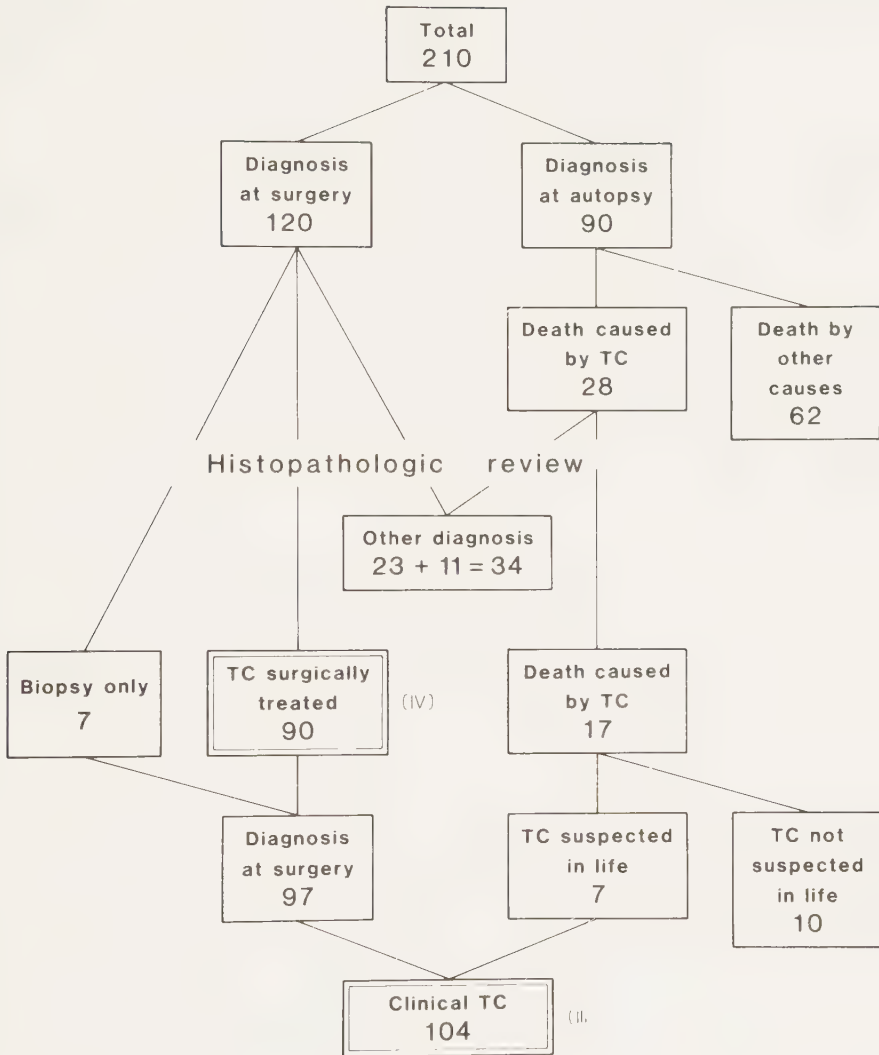


Fig 1: New diagnoses of TC in Malmö 1960 - 1977.

Table I: Histopathologic diagnoses in 100 consecutive patients surgically treated for a thyroid nodule, solitary by palpation.

Malignant tumor	18
Follicular adenoma	41
Colloid goiter	40
Thyroiditis	1

death. The remaining 148 cases were reviewed and reclassified. After revision, 34 cases were excluded because the thyroid tumors were interpreted as benign or as metastases from other malignant tumors. In seven of the revised 17 autopsy cases the TC diagnosis was suggested *intra vitam*; these seven cases were therefore included in the study, together with 97 revised surgical cases.

IV. Out of the 97 patients in whom the revised histologic diagnosis of TC was based upon surgical specimens (fig 1), seven were excluded because the only surgical intervention had been a biopsy, thus leaving 90 patients for evaluation.

III + IV. Information about history, symptoms and signs, diagnostic results, treatment and postoperative complications, was collected retrospectively from hospital records. The patients were followed to the closing date of the study, December 31, 1979. Patients followed personally all had a clinical examination, chest X-ray and laboratory screening. Patients examined elsewhere, generally had a clinical examination with laboratory screening once or twice a year and chest X-ray once a year or every two years.

V. The intention was to include all individuals who had died in Malmö between 1960 and 1977 from TC or from side effects of treatment for TC.

The cases were searched for in the autopsy registry at the Department of Pathology. Altogether 49 cases were found but eleven were excluded after histopathologic revision as being metastases from other malignant tumors, leaving 38 cases for evaluation. Eighteen of these were also included in the study of clinical TC (III).

III, IV, V. The histopathologic classification of thyroid tumors was made according to WHO (19). Only malignant epithelial tumors were included. Tumors diagnosed primarily as small cell anaplastic carcinomas were considered as malignant lymphomas and excluded.

The investigation period was divided into three parts each of six years: period I 1960-1965, period II 1966-1971 and period III 1972-1977.

STATISTICAL METHODS

Incidence was considered to follow a Poisson distribution, and tests of statistical differences between incidence density rates were made according to Cox (44). The ManWhitney rank sum test for unpaired observations was used in tests of statistical difference between thyroglobulin values. Survival was estimated according to the life table method (45). Figures for expected survival were calculated using information on the mortality rate for the Malmö population 1970 to 1974. Relative survival rate was defined as the ratio between the observed survival rate and the expected survival rate (46). 95% confidence limits and statistical differences between survival rates were calculated according to Colton (47). In other statistical calculations the chi square test was used. P values less than 0.05 were considered as indicating statistical significance.

DISCUSSION OF MATERIAL AND METHODS

I. About one third of the women who were selected at random from the city council registry and invited for the health screening program (which included examination for thyroid disease) did not accept the invitation. Among these, 95 were selected at random to answer a questionnaire on thyroid disease, and 61 answered after up to two reminders. The prevalence of anamnestic thyroid disease among these "non-participants" was found to be about 6% higher than among the participants in the study. The difference was not significant but it was assumed that the prevalence of thyroid disease found in the participant group was not an overestimation of the prevalence in the corresponding population.

The women found to have goiter at the primary screening also underwent a second examination by another physician. Lack of concordance between the observers occurred in three out of 47 cases and it was concluded that this variation was modest compared with that found by other authors (48).

II. The patient material in this study was, by nature, highly selected. The results of physical examination and thyroid scan, and the cytological findings, had been used to select patients for surgery among all patients presenting with nodules solitary by palpation. In particular, thyroid scans showing "a solitary cold spot" and/or a cytology report indicating malignancy or true neoplasm were considered to implicate an increased possibility for malignancy.

III, IV, V. The population of Malmö has been found suitable for epidemiological studies (49-52). It is demographically well defined and is served by only one general hospital. The autopsy frequency was high which should provide a reliable basis for the causes of death. Concerning cancer diseases, one further condition facilitates such studies, *i.e.* the fact that in Sweden all cancer cases are notifiable to the National Cancer Registry.

Information from the Swedish Cancer Registry on thyroid cancer in the community of Malmö was available for the period 1960 to 1974. This information was checked with the diagnoses recorded in the registries at the Department of Pathology, Surgery and ENT. Only two patients with verified clinical TC during this period were not recorded in the Swedish Cancer Registry, which indicates an effective reporting system.

It might be objected that the follow-up time for patients with a clinical diagnosis of TC (III) is too short for a correct estimation of the prognosis. Using the life table method to estimate the survival rate, it is partly possible to compensate for this because it enables one to use all survival information on the closing date of the study (46). The reliability of the method, however, presupposes that the survival experience for late entries in the study after the closing date is similar to that of patients under observation for the entire period (53). Since this is not quite true for patients with differentiated TC during the first five to six years of observation (cf. fig 3), late entries in the present study could lead to a slight overestimation of the survival rate.

Results and comments

A. Epidemiological aspects

1 PREVALENCE OF PALPABLE THYROID DISORDERS (I, II)

On physical examination a palpable goiter was found in 54 of 477 middle-aged women (11.3%). Palpable solitary nodules were present in 31 women (6.5%), multiple nodules in 17 and diffuse enlargement in six. One of the solitary nodules was more than 3 cm in diameter; 21 had diameters less than 2 cm.

Twenty-seven of the 31 women with a solitary nodule accepted a second examination comprising thyroid scintigraphy and a fine-needle aspiration biopsy. Malignancy was suspected in one case, because the cytology report indicated Askanazy cell tumor; this woman was treated by hemithyroidectomy and the histopathologic examination following surgery revealed colloid goiter but no tumor. In the remaining 26 patients the results of the second examination were considered a sufficient basis for benign diagnosis and no further patients were treated surgically.

Eight of the participants in study I had previously been surgically treated for atoxic goiter; at histopathologic examination following surgery two had been found to have follicular adenoma and six colloid goiter. None had been treated for TC.

The male/female ratio in the 100 patients with solitary nodules selected for surgical treatment (II) was 1:6. Twenty-eight patients were below 40 years of age, 46 aged 40-59, and 16 aged 60 or more.

COMMENTS

The present findings are considered to be valid only for the middle-aged female population, and the prevalence of goiter and palpatory solitary

nodules agrees well with the findings in other non-endemic areas (48,54). The age and sex distribution, as found in study II, can be accepted only with caution due to the selective nature of the material. The sex ratio of 1:6, however, is similar to that (1:5) found in individuals with a solitary nodule in an unselected middle-aged American population (55). The proportion of patients with solitary nodules aged 60 or more is probably smaller than the corresponding proportion in the general population, because aged patients are less likely to have surgery than younger ones, particularly in the case of mild disorders like thyroid nodules. In a population survey in Britain, the frequency of visible goiter was found to decrease after the age of 50, but the frequency of nodular goiter actually increased with age, also after the age of 60 (54).

2 PREVALENCE OF THYROID CARCINOMA (III, V)

Approximately 31,000 clinical autopsies were performed in Malmö during the 18-year period of investigation. After histopathologic review, TC was considered the cause of death in 38 of these cases. In a further 65 cases a diagnosis of TC was made but considered an additional finding at autopsy without relevance to the cause of death. These figures together amount to a frequency of TC at autopsy of 0.33%. In ten of the fatal cases and in 62 of the cases where TC was an additional finding, the TC diagnosis was made *post mortem*. Twenty of these 62 thyroid tumors ranged between 1 and 4 cm in diameter, the remaining 42 tumors were all less than 1 cm.

COMMENTS

The prevalence of clinically detectable TC could not be established in study I because the number of participants was too small. Most patients with severe malignant diseases, as for instance anaplastic TC, come to medical attention sooner or later, and a good estimate of the prevalence can usually be obtained from incidence figures. This is not necessarily true for individuals with differentiated TC due to the indolent character of the disease. Consequently, a considerable number of individuals in the population probably have clinically unsuspected TC and the annual

incidence can be expected to be considerably lower than the prevalence. An indirect expression of this is given by the surprise findings of TC in the clinical autopsies: the twenty TC:s among the cases where TC was an additional finding that were larger than 1 cm may have been palpable *intra vitam*; at least some of the ten fatal cases should also have been possible to diagnose in life. This is equivalent to a frequency of about 90 cases of TC in 100,000 autopsies, which should have been presumptively detectable *intra vitam*. Such a figure is of course not applicable to the general population due to the selective nature of the autopsy material and the uncertainty in determining which tumors are possible to track down in life. The assumption that the prevalence of TC is considerably higher than the annual incidence is, however, supported by an extensive population survey in Nagano, Japan, where about 59,000 individuals were examined by palpation of the neck (7). Altogether, the prevalence of TC was 129 per 100,000, the prevalence in women was 186, in men 60. The prevalence of TC was found to be approximately 90 times the annual incidence of TC in Japan.

The prevalence of TC in autopsy series has been shown to increase the more carefully the thyroid glands are examined, *i.e.* the more slices that are cut from each gland (56). The present finding of TC:s in 0.33% of the routine autopsies is thus low compared to thoroughly examined series. In a recent report from Malmö by Bondeson and Ljungberg, a prevalence of TC of 8.6% was found in 500 consecutive autopsies (6). The majority of the tumors was below 5 mm in diameter and the papillary types of carcinoma were most frequent. One interesting finding was that the male/female ratio was approximately 1:1, another that the frequency of carcinomas did not seem to increase with increasing age. Most of these small carcinomas apparently remain undiagnosed in life. They may, however, come to the attention of the clinician when they are revealed as incidental findings at thyroid surgery. The frequency of this depends, besides on the true prevalence of small TC:s and the frequency of thyroid operations, obviously also on the carefulness of the histopathologic examination of the surgical specimens.

3 INCIDENCE AND MORTALITY RATE OF TC IN MALMÖ (III, V)

The average incidence of clinical TC in Malmö for the period 1960 to 1977 was 2.4. The figure for females was 3.4, for males 1.3; the male/female ratio was accordingly 1:2.9. In period III the age standardized incidence of differentiated TC was 2.7, which was significantly higher than in period I (1.8) and period II (1.6, $p < 0.05$).

The average mortality rate in Malmö for the same period of time was 0.9. The ratio between men and women was 1:1.4. The age standardized mortality rates in the periods I, II, and III were 1.3, 0.7, 0.8, respectively. The difference between the rates was not significant.

The age specific incidence for the 104 patients with clinical TC (III), contrasted with the age specific incidence (age at diagnosis) for the 38 patients in whom the disease was fatal (V), is given in figure 2.

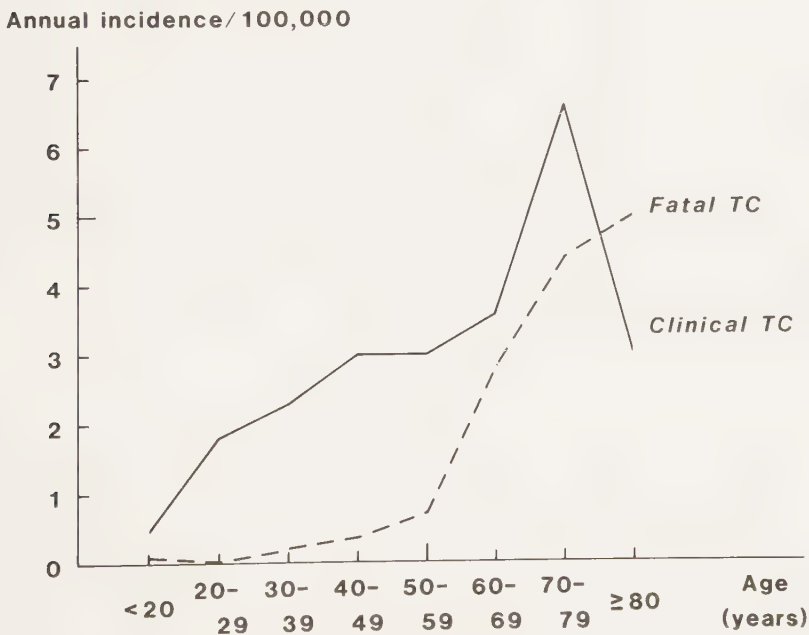


Fig 2: Age specific incidence (age at diagnosis) in 104 patients with clinical TC, and in 38 patients in whom the TC was fatal.

It seems that relatively few patients with a diagnosis of TC before the age of 60 die from the disease whereas TC diagnosed after this age is increasingly often fatal.

COMMENTS

The incidence of 2.4 in the present study was lower than the average incidence (3.6) in whole Sweden during the same period of time, as given by the National Cancer Registry (57). The main explanation of this difference is considered to be methodological: firstly, incidental autopsy findings are included among the cases reported to the Cancer Registry; secondly, histopathologic review will change many diagnoses from malignant to benign, as recently shown by Saxén et al (34) and confirmed in the present study (fig 1). Our average incidence figure of 1.95 for the sixties was very close to that (1.8) found by Franssila et al for all Sweden in 1960 after histopathologic review and exclusion of autopsy cases (58). The increased incidence during the later part of the present study is in accordance with a rising incidence in all Sweden, although the increase was not as pronounced as in Malmö. The age standardized mortality rate, on the other hand, did not change significantly during the period of investigation; also, in all Sweden the mortality rate was fairly stable during the same period of time (59). One possible explanation of the difference in trend between incidence and mortality rate might be that more relatively benign cancer tumors were diagnosed during the later years because of increased health awareness. This explanation is supported and further commented in sections B 3 and C.

It is a general observation that a diagnosis of TC is proportionally more common in young individuals than is the case for many other cancer forms. Thirty per cent of the TC:s in the present study (III) thus occurred in persons below the age of 40. The corresponding rates for Sweden in 1977 were for the following tumor types according to official statistics: breast cancer 5%, gastric cancer 1%, and lung cancer 1% (57). The age specific incidence of patients with TC in whom the disease was fatal was, on the other hand, more close to that observed in other cancer diseases

(fig 2). This means that young age at diagnosis should be a favorable prognostic factor, an observation that has also been made by several other authors (26,30,60). When interpreting figure 2 it is important to take into consideration that surprise findings of fatal TC made at autopsy (ten cases) were not included in the conception of clinical TC. In fact, this can explain why the incidence curve of "fatal TC" after the age of 80 exceeds the incidence curve of "clinical TC".

The mortality rate from TC for the whole of Sweden was, on an average, 1.3 during the period 1960 to 1977 according to official death statistics (59). The corresponding figure for Malmö found in the present study was 0.9. The difference in mortality rate is probably due to inclusion in the official figures of patients not dying from TC. The number of cases of fatal TC in the present study was reduced by approximately 20% at the histopathologic review. It is therefore assumed that official figures for mortality rates of TC may be overestimations of true mortality rates.

4 FREQUENCY OF TC IN PALPABLE SOLITARY NODULES (I, II)

The frequency of TC in 100 palpable solitary nodules in the patients selected for surgical treatment was 18%. Malignant tumors composed 29% of all diagnoses in men, while the corresponding figure for women was 16%. In patients below the age of 40 the frequency of TC was 14% corresponding to 13% in patients aged 40 to 59, and 44% in patients aged 60 or more.

COMMENTS

The frequency of TC in solitary nodules of 18% is probably a gross over-estimation of the corresponding frequency in the general population because the patient material was highly selected. Let us assume that the prevalence of palpable TC in middle-aged women in Malmö is the same as in Nagano, Japan (7), that is 180 per 100,000 women. In the present study (I) the prevalence of palpable solitary nodules was 6.5% (middle-aged women). This then means that palpable TC would make up approximately 3% of all solitary nodules in middle-aged women provided that palpable TC always

appears as a solitary nodule. The differences between the sexes and between the age groups in frequency of TC in solitary nodules (II) may to some extent reflect the proportions in the population. The sex differences can mainly be explained by the fact that the male/female ratio in benign solitary nodules is considerably lower than in TC. The higher frequency of TC in patients aged 60 or more is suggested to be due in part to the increase of TC incidence, in part to a stricter selection of patients for surgery in this age group.

B. Etiology and clinical evaluation

1 FAMILIAL DISPOSITION (I, II, III)

Six out of 104 patients with TC were familial, occurring among first degree relatives (*i.e.* parent, child or sibling) in three apparently unrelated families. In two cases the mother and her son/daughter had papillary TC, in the third case the mother had anaplastic TC, her daughter follicular TC. In study II, one patient with papillary TC was found because her mother had previously been treated for a combined medullary and papillary carcinoma.

The frequency of benign goiter in the family was estimated in paper I. Of the women found to have goiter 26% revealed familial occurrence of goiter, while the corresponding frequency among non-goiterous women was 9%. The difference of 17% was significant ($p < 0.01$).

Benign goiter in blood relatives occurred in 11% among 18 patients with TC, and in 46% among 82 patients with benign thyroid disorders (II). The difference of 35% was significant ($p < 0.01$).

COMMENTS

One of the most clearly defined inherited thyroid disorders is medullary carcinoma when it occurs as part of a multiple endocrine neoplasia syndrome (MEN type 2) which also includes multiple pheochromocytoma and sometimes multiple neural tumors (61). The mode of inheritance has been found to be autosomal and dominant (62). Two cases of MEN type 2 were found in the present study at autopsy (V). Later screening of the relatives to one of these cases unveiled further instances of the syndrome. There is increasing evidence to suggest that papillary TC may occasionally also be inherited (63,64). This suggestion was supported by the present study where three "couples" of parent-offspring were found. It is evident that some familial, probably genetic, factor plays a role in the development of benign goiter. The mode of inheritance has, however, not been defined. It has been suggested that the underlying mechanism may be a genetically conditioned susceptibility for developing this condition which is likely

to be under the influence of more than one gene locus (65). In the present study it appears that blood relatives to patients with TC show almost the same frequency of benign goiter as blood relatives to individuals without goiter (11% vs 9%).

Information about heredity might to some extent be used in evaluation of patients with suspected thyroid nodules. This is particularly true when medullary or papillary TC occurs in the family, but information on benign goiter in the closest family may also be useful to support a benign diagnosis.

2 IRRADIATION TO THE NECK (III, II)

A history of irradiation to the neck for benign disorders, including goiter, in childhood and adolescence was revealed in 7% of the patients with TC in Malmö (III). Six patients had a diagnosis of papillary carcinoma, while one 47-year-old woman had anaplastic carcinoma. One of the patients, surgically treated for a solitary thyroid nodule (II) gave a history of irradiation in childhood; histopathologic examination following surgery showed papillary carcinoma.

COMMENTS

There are several indications that irradiation therapy may be one etiologic factor in the development of benign as well as malignant thyroid disorders (66). Irradiation to the neck for benign disorders such as acne, thymus enlargement, and tuberculous adenitis was widely used in the USA from the early 20s to the late 50s, and in one study this was held responsible for a reported five-fold increase in TC incidence (67). Irradiation to the neck has not been as commonly used in Sweden as in the USA; thus, among 477 middle-aged women in Malmö (I) none reported having had such a treatment in childhood or adolescence. The frequency of 7% with a history of neck irradiation among the TC patients in the present study is low compared with American series, where corresponding frequencies of up to 40% have been reported (66,68). The difference in the incidence of radiation

exposure between Sweden and the USA may be one explanation for some of the differences in, for instance, distribution of histological types of TC, and in prognosis, between the present and American materials.

3 PRESENTING SYMPTOMS (III)

A lump in the neck was the only symptom in 66% of the patients with a clinical diagnosis of TC. Thirty per cent of the patients came under medical care because of symptoms of local tumor growth such as pressure, hoarseness, and air-way obstruction, or because of symptoms of metastases. The remaining four per cent represented incidental findings at operations for thyrotoxicosis or hyperparathyroidism.

In 36% of the patients with a lump in the neck as the only symptom, this lump was discovered at clinical screening or at clinical examination for other complaints.

A thyroid lump as the only symptom was significantly more frequent in the last six-year period of the study ($p < 0.05$), whereas the frequency of the other presenting symptoms was unchanged during the years studied.

COMMENTS

The classification of the presenting symptoms used here reflects to some extent the tumor stage at admission to hospital. The most indolent, but clinically palpable, tumors are probably to be found in patients with a thyroid lump as the only symptom, while tumors incidentally revealed at neck operations for non-malignant thyroid diseases or other conditions such as hyperparathyroidism, are probably an expression of the high prevalence of occult carcinomas, as found in autopsy studies (4,6). An increasing number of TC was incidental clinical findings (cf Definitions) during the period of investigation; this, in fact, was the main reason why the symptom "thyroid lump" was more frequent in period III than in the two preceding periods. It is suggested that these clinically incidental findings reflect the health care situation rather than the prevalence of

TC. Improved health awareness and availability of medical care in recent years may help to explain the increased incidence of TC in the last six years of the present investigation (section A 3).

4 HISTORY AND PHYSICAL EXAMINATION (II, III)

The size, extent of fixation, growth, and length of history in 100 thyroid nodules, solitary by palpation, were related to the histopathologic diagnosis (malignant or benign) following surgery (II). Nodules found to be hard on palpation (eleven cases) were significantly more malignant (seven cases) than benign (four cases) ($p < 0.001$). Four nodules were fixed to surrounding tissue; three of these were malignant, one benign (in a patient previously operated on for goiter). Size or growth rate of the nodule or clinical duration were not correlated significantly to malignancy.

Of the 104 patients with a diagnosis of TC (III), the malignant diagnosis was clinically obvious or strongly suspected in 24, due to rapidly growing goiter (five), enlarged neck lymph nodes (ten), or distant metastases (nine). Sixty-one patients had a solitary thyroid nodule as the only sign, whereas 18 showed diffuse or multinodular goiter.

COMMENTS

Physical examination and anamnestic information are often sufficient to suggest a malignant diagnosis in a case of a rapidly growing anaplastic carcinoma or in cases with metastases. Such cases, however, comprised only about one fourth of all carcinomas in the present study. The physical examination is apparently of limited value when a TC appears as a solitary nodule, which is the most common presenting sign. The finding of nodules hard on palpation or fixed nodules, may be one indication for surgical excision. Other authors have reported a high incidence of TC in growing nodules in patients on thyroxine therapy (69) and have recommended excision of such nodules. The validity of such a policy could not be evaluated in the present study.

5 THYROID SCAN (I, II, III)

The percentage distribution of the scintigraphic findings in subjects with a thyroid nodule, solitary by palpation, in studies I, II, and III, is shown in table II. Twenty-two per cent of the patients with a solitary cold nodule had TC, whereas 15% with multiple nodules on the scintigram had both thyroid carcinoma and multinodular goiter (II). Thyrotoxicosis was the indication for surgery in all patients with a "solitary hot nodule" (II); TC was not diagnosed in any of these, neither was it diagnosed in any of the patients where the scan was normal (II). None of the women in study I had TC.

Table II: Percentage distribution of the results of thyroid scan in patients with a nodule, solitary by palpation. Comparison between patients with known TC (III), patients referred for surgery (II), and unselected middle-aged women (I).

Thyroid scan	Palpatory solitary nodule		
	III n=59	II n=96	I n=27
Cold solitary	86	61	7
Hot solitary	0	13	11
Multiple	5	14	33
Normal	9	12	49
	100	100	100

COMMENTS

It is well documented that the majority of malignant thyroid nodules appears as a "solitary, cold spot" on scintigram (70). This was supported in the present study, where the finding of "a solitary cold spot" made up 86% of all scintigraphic findings in those patients with TC who had a solitary nodule as the presenting sign. Benign thyroid disorders, such as adenomas or solitary colloid nodules, on the other hand, also frequently

appear as a "solitary cold spot" on scintigram. The frequency of 22% of TC in solitary cold nodules in the present study (II) is in good agreement with the results from other series (70,71) and should be fairly representative for the general population in a non-endemic area, provided that all subjects found to have solitary cold nodules have been treated surgically.

The statement that malignancy is unlikely in patients with a "solitary hot spot" on scintigram (70,72) was supported by our study: no such patient was found to have TC. A scintigram showing alternating hot and cold parts (multiple in table II) is often interpreted as indicating multinodular goiter. However, in rare instances TC is diagnosed in patients with such a scintigram, *i.e.* when the cancer arise in a multinodular goiter or when the cancer is multiple. Examples of both these situations occurred in the present study (table II). A normal scintigram in patients with a solitary nodule has also to be interpreted with some caution, since small, non-functioning carcinomas may be hidden by over- or underlying functioning thyroid tissue (73).

The degree of usefulness of the scintigraphic method in differentiating between benign and malignant nodules can best be seen in the results obtained in the study of women from the unselected population (I). The suspicion of malignancy could be dismissed in 11% (solitary hot changes) and considerably reduced in a further 33% (multiple changes). If suspicion of malignancy remains after a scintigraphic examination indicating multiple changes, additional evaluation should be done, such as aspiration fine-needle biopsy.

6 ASPIRATION BIOPSY CYTOLOGY (I, II)

The distribution of the cytologic findings in patients selected for surgical treatment because of a palpable solitary thyroid nodule (II), and in women with the same sign found in the population survey (I), is presented in table III. One woman in study I had a cytologic diagnosis of suspected neoplasia but histopathologic examination following surgery showed colloid goiter.

Table III: Percentage distribution of the cytologic findings in patients with a thyroid nodule, solitary by palpation. Comparison between patients referred for surgery (II) and unselected middle-aged women (I).

Cytologic findings	Patients with a palpable solitary nodule	
	II n = 98	I n = 27
Malignant	4	0
Neoplasia NOS ¹⁾	37	4
Benign	48	85
Insufficient for diagnosis	11	11
	100	100

1) NOS: not otherwise specified, i.e. malignancy neither proven nor ruled out.

Among the patients surgically treated (II) four had a cytologic diagnosis of papillary carcinoma and the same diagnosis histopathologically (table IV). The cytologic diagnosis was benign (colloid goiter) in a woman with a final diagnosis of papillary carcinoma. This patient had a deeply situated, large recurrent cancer with an overlying colloid goiter representing the index nodule from which the cytologic aspirate was obtained. One of the eleven patients, having cytologic material insufficient for diagnosis, had a follicular carcinoma with a large central calcification.

COMMENTS

There were no false positive cytologic diagnoses in the present study (II), a finding that is in agreement with statements in other reports (12,13). It is, however, impossible for the cytologist to differentiate between, on the one hand, papillary and follicular carcinoma, and on the

Table IV: The results of fine-needle aspiration biopsy cytology in 98 patients with a palpable solitary thyroid nodule related to the histopathologic diagnoses following surgery.

Cytologic diagnosis	Histopathologic diagnosis			
	Malignant (n = 18)	Follicular adenoma (n = 40)	Colloid goiter (n = 39)	Thyroiditis (n = 1)
Malignant (n=4)	4			
Neoplasia NOS ¹⁾ (n=36)	12	20	4	
Benign ²⁾ (n=47)	1	14	31	1
Sample insufficient for diagnosis (n=11)	1	6	4	

1) NOS: not otherwise specified, i.e. malignancy neither proven nor ruled out. Includes 14 cases of "neoplasia suspected".

2) Colloid goiter (n=46) or thyroiditis (n=1).

other hand follicular adenoma, if typical cytologic features of papillary carcinoma, such as papillary forms of the tumor fragments or pseudonucleoli, are missing (13). A final diagnosis of malignancy in cases of thyroid nodules with a cytologic appearance of neoplasia (table IV) often requires multiple sections of the thyroid capsule (74). Therefore, all such nodules should be excised for histopathologic examination.

It is apparent from table III that the cytologic findings are benign (colloid goiter or thyroiditis) in the great majority of unselected individuals with a solitary thyroid nodule. Surgical excision of solitary nodules

in which the cytologic diagnosis is benign might thus be avoided in many cases provided the accuracy of a benign cytologic diagnosis is sufficiently high. It may be difficult in cytologic (as well as in histopathologic) diagnostics to separate cases of follicular adenoma from cases of colloid goiter (75). This was reflected in the present study by the fact that 14 patients with a cytologic diagnosis of colloid goiter had a histopathologic diagnosis of follicular adenoma (table IV). There was also a certain variation between the two cytologists who reviewed the cytologic slides in the distinction between colloid goiter and neoplasia. This variation, however, only occurred in cases with a final diagnosis of adenoma or colloid goiter. The accordance in the cytologic classification was complete in all 18 cases of malignant tumor. One patient with a benign cytologic diagnosis had a papillary carcinoma, but the index nodule did not, in this case, correspond to the underlying cancer.

It is concluded that

- a cytologic diagnosis of malignant tumor is accurate.
- a cytologic diagnosis of neoplasia almost always indicates a malignant tumor or a follicular adenoma. Such a diagnosis should lead to excisional biopsy.
- the reliability of a benign cytologic diagnosis is high provided the cytologic sample is representative of the underlying pathological change.

7 SERUM THYROGLOBULIN (Tg) (II, I)

The Tg-values obtained preoperatively were significantly higher in the 18 patients with malignant tumors than in the 82 patients with benign disorders (II) ($p < 0.01$). Using the reference value recommended in Malmö ($Tg < 40 \mu g/l$), the sensitivity of the test was calculated to 83%, the specificity to 46%. Three patients with TC and two with toxic adenoma had Tg-values above $500 \mu g/l$.

Thirty per cent of the women with palpable goiter had Tg-values $\geq 40 \mu g/l$ which was significantly more than the corresponding figure (12%) for women without thyroid disease (I) ($p < 0.001$).

COMMENTS

Radioimmunoassays for accurate determinations of Tg in serum have been available since about a decade (43,76). Elevated Tg has been found in most thyroid disorders (77,78), but the highest values are usually found in patients with metastases from differentiated thyroid carcinoma (79) and in patients with thyrotoxicosis (78,80). The utility of the test in the follow-up of patients treated for thyroid carcinoma is well documented (81,82), whereas reports of its diagnostic value are scarce. In contrast to Schneider et al (83) we found that the Tg-values in patients with thyroid malignancy were significantly higher than in patients with benign disorders. The predictive value of the test was, however, low. Values of Tg above 500 $\mu\text{g/l}$ only occurred in patients with either thyroid cancer or with thyrotoxicosis. Considerably elevated Tg-values in patients with a solitary thyroid nodule but without thyrotoxicosis therefore seem to support a diagnosis of thyroid cancer.

C. Histopathology

The distribution of the primary tumors by histologic type is shown in table V. Ten of the fatal cases were surprise findings at autopsy (cf fig 1). Papillary TC was the dominating histologic type in the clinical materials, whereas anaplastic carcinoma was the most frequent one in the autopsy cases. The four medullary carcinomas in study III (and IV) were all solitary and apparently non-familial, whereas two of the autopsy cases, as mentioned earlier, were parts of a MEN syndrome. The 14 anaplastic tumors, two of which were surprise findings at autopsy, were all of the giant cell type. Nine of the anaplastic carcinomas also contained elements of differentiated TC; five of these were follicular in type and four were papillary.

Table V: Distribution by histologic type of 104 cases of clinical TC, 90 cases of surgically treated TC, and 38 cases of fatal TC in Malmö 1960 - 1977.

Histologic type	Clinical TC (III) n = 104	TC surgically treated (IV) n = 90	Fatal TC (V) n = 38
Papillary	66 (63%)	65 (72%)	10 (26%)
Follicular	22 (21%)	20 (22%)	10 (26%)
Medullary	4 (4%)	4 (4%)	4 (11%)
Anaplastic	12 (12%)	1 (1%)	14 (37%)

Microscopic foci of papillary carcinoma in a grossly normal thyroid lobe were found in three of 17 patients (18%) treated by total thyroidectomy for macroscopic unilateral papillary TC.

The mean age and age range at diagnosis for patients with clinical diagnosis of TC (III) and for patients in whom the TC was fatal are contrasted in table VI. In the patients with a clinical diagnosis of papillary and folli-

cular TC the mean age was 15 and 17 years respectively, below the corresponding mean ages for patients with fatal TC.

Table VI: Age at diagnosis for 104 patients with clinical diagnosis of TC (III) and 38 patients in whom the TC was fatal.

Histologic type	Mean age and age range at diagnosis	
	Clinical TC n = 104	Fatal TC n = 38
Papillary	49 (15-79)	64 (35-79)
Follicular	53 (16-75)	70 (53-82)
Medullary	49 (37-59)	48 (14-68)
Anaplastic	75 (46-89)	75 (46-89)

In table VII the distribution by size and extension of the primary tumor for patients with a clinical diagnosis of papillary and follicular TC is contrasted with the corresponding distribution for patients who died from papillary and follicular TC. The 14 anaplastic carcinomas were all extra-thyroidal; node metastases were present in ten of them, distant metastases in 13. One of the four medullary carcinomas belonging to the group of clinical TC was occult, the remaining three were intrathyroidal.

Thirteen of the 25 occult tumors in study III were incidental findings at operation, six were clinically palpable, five patients presented with lymph node metastases and one with bone metastases. Node metastases had been present at the presentation in all three autopsy cases with a primary diagnosis of occult papillary TC (table VII).

Table VII: The distribution of papillary and follicular carcinoma by size and extension of the primary tumor at diagnosis in 88 patients with clinical TC and in 20 patients who died from TC.

Tumor extension	Clinical TC (III)		Fatal TC (V)	
	Papillary n = 66	Follicular n = 22	Papillary n = 10	Follicular n = 10
Occult	23	1	3	0
Intrathyroidal	23	14	1	3
Extrathyroidal	20	7	6	7
Node metastases	29 ¹⁾	2	5	3
Distant metastases	1	4	1	6

1) Occult cancer 7 (30%)

Intrathyroidal 7 (30%)

Extrathyroidal 15 (75%)

The incidence of intrathyroidal carcinoma was significantly higher during the last six years of the study (period III) than during the two preceding periods ($p < 0.01$), whereas the incidence of occult and extrathyroidal carcinoma did not differ significantly. The relative distribution of the histologic types did not change significantly during the years studied.

COMMENTS

The present figures for clinical TC, with respect to histologic type and tumor stage, are considered representative of a non-endemic area with a high level of medical care. The relative distribution of the histologic types remained unchanged during the years of investigation, whereas a marked change in the distribution of tumor stages was noted during the last six-year period of the study: the number of intrathyroidal tumors more than doubled compared with the two preceding periods, while the number of occult and extrathyroidal tumors remained on the same level. This finding is in

accordance with the increase in the same period of the number of patients with a thyroid lump as the only presenting sign, as described previously. The higher incidence of differentiated TC in period III (see section A 3) can thus be explained by the fact that more intrathyroidal carcinomas, appearing as thyroid nodules without other symptoms, were diagnosed. It was suggested earlier that such tumors might be more common in the population than indicated by the annual incidence of TC. This paves the way for the possibility that increased health awareness and availability of medical care might have resulted in a higher detection rate of TC, and that this, rather than an increase in prevalence, is the explanation of the higher incidence in Malmö during the 1970s. Another explanation might have been a more careful histopathologic examination. This would probably implicate a relatively higher proportion of follicular carcinoma and incidentally discovered tumors, since the detection of such cases is strongly dependent on the number of tissue blocks taken from each specimen (56,74). Since the relative number of these tumors remained unchanged during the period of investigation, changes in histopathologic procedures are not considered to be the explanation of the higher incidence in period III.

About two thirds of the anaplastic carcinomas contained elements of differentiated TC. Moreover, a goiter had been noted in five of the 14 patients with anaplastic tumors for a varying number of years before the anaplastic carcinomas killed the patients. These facts support earlier suggestions that anaplastic carcinoma may develop from differentiated TC (84,85,86).

The mean ages at diagnosis were considerably higher for patients dying from papillary and follicular TC than the corresponding mean ages for all patients with a clinical diagnosis of these tumors. Thus, it seems that the increasing mortality from TC with age described earlier (fig 2) is not solely due to a late onset of anaplastic TC (only two such cases were diagnosed before the age of 60), but also to a higher mortality in older than in younger patients with papillary and follicular TC.

The distribution by histologic type of TC in the present material and the corresponding distribution in the Nordic countries as found by Franssila et al (58), are compared in table VIII. Our figures seem to agree best with

Table VIII: Annual incidence and percentage distribution of TC by histologic type in four Nordic countries and in Malmö

Histologic type	Franssila et al 1981 (58)				
	Finland	Iceland	Norway	Sweden	Malmö
	1959-61	1955-68	1959-60	1960	1960-77
	n = 152 (1.0) ¹	n = 129 (4.0) ¹	n = 148 (1.6) ¹	n = 190 (1.8) ¹	n = 104 (2.4) ¹
Papillary	38	67	65	46	63
Follicular	25	9	15	20	21
Medullary	6	8	2	5	4
Anaplastic	24	12	16	26	12
Other	7	4	2	3	0
	100	100	100	100	100

1) Age adjusted annual incidence per 100,000

the findings in Iceland and Norway. Iceland, and to a great extent also Norway, like Malmö are considered free from endemic goiter, whereas in some districts in Sweden and Finland goiter probably still is endemic. The detection rate of differentiated TC is probably lower in areas where goiter is endemic than in areas without goiter, since indolent thyroid tumors in endemic areas are likely to be hidden (and thus undiagnosed) among all benign goiter nodules. This, together with the fact that the papillary type of tumor is probably more frequent in undetected palpable TC than in clinically diagnosed TC (7), and the different occurrence of endemic goiter in the other areas examined might in part explain the differences in incidence and in distribution by histologic type between these areas. The higher proportion of follicular cancer in Finland compared to the other Nordic countries and Malmö was not due to a higher incidence of this tumor type there; the incidence of follicular carcinoma in Iceland

was actually higher than in Finland. This contradicts earlier suggestions of a causal relationship between benign goiter and follicular carcinoma (87). The high incidence of papillary TC in Iceland compared with the other areas is probably not solely due to a higher detection rate, since also the mortality rate from papillary carcinoma has been found to be higher in Iceland (58). Williams et al have suggested that iodine might be one etiologic factor in the development of papillary TC, and that the rich iodine supply in Iceland can in part explain the high incidence of this tumor there (88).

Table IX shows the various compositions, as to the histologic types of TC, of some selected materials in comparison with the present one. The differences in distribution of the tumors by histologic type may to some extent be explained by different selection mechanisms and differences in histopathologic diagnostic criteria, but also by such factors as differences in radiation exposure in childhood, collection of cases during different time periods (with different detection rates), and by true geographical differences for unknown reasons.

Table IX: Percentage distribution of TC by histologic type in selected series

Histologic type	Frauenhoffer et al (30) USA 1959-1969 ¹ n = 97	Woolner et al (25) USA 1926-1955 ¹ n = 885	Beaugié et al (26) Britain 1945-1972 ¹ n = 158	Staunton et al (33) Britain 1931-1963 ¹ n = 397	Heitz et al (89) Switzerland 1945-1975 ¹ n = 550	Present series Malmö 1960-1977 ¹ n = 104
Papillary	90	61	51	37	26	63
Follicular	6	18	20	18	41	21
Medullary	1	6	9	3	2	4
Anaplastic	3	15	20	42	27	12
Other	0	0	0	0	4	0
	100	100	100	100	100	100

1) Time period for collection of patients

D. Treatment

1 SURGICAL TREATMENT AND ADDITIONAL THERAPY (IV)

Ninety patients from Malmö were surgically treated for TC during the period of investigation (fig 1). The distribution of the tumors by histologic type appears from table V. Total thyroidectomy was performed in 30 patients, lobectomy in 47, and thyroid resection in 13. Excision of lymph node metastases was made in 24 cases.

The distribution of the types of surgical procedures diverged markedly between the first twelve-year period and the last six-year period of the study. This was due to a change in policy from a conservative to a more radical approach. Thus, 27% of the total thyroidectomies were performed before 1972 whereas 72% of the lobectomies were performed during the same period of time.

In 78 patients the surgical treatment was considered to be for cure. The procedures for curatively treated patients with papillary and follicular carcinoma for each of the tumor stages *occult*, *intrathyroidal* and *extra-thyroidal* are shown in table X. Three patients with intrathyroidal medullary carcinoma were treated by total thyroidectomy, the fourth medullary carcinoma (*occult*) was an incidental finding after a thyroid resection for thyrotoxicosis.

Twelve patients were operated for palliation. Four of these had distant metastases at presentation; all four had a total thyroidectomy which was considered locally radical. In eight patients the operation was palliative because of inextirpable local growth (seven cases) or regional lymph node metastases (one case).

All patients were postoperatively given thyroxine in a TSH-suppressive dose. Postoperative therapy with external irradiation was given to five patients treated for palliation and to two treated for cure. An ablative dose of ^{131}I was given to patients treated by total thyroidectomy if the thyroid scan performed three to four weeks postoperatively showed an

Table X: Tumor stage and type of surgical procedure in 59 patients with papillary and 15 patients with follicular cancer in whom the operation was for cure.

SURGICAL PROCEDURE	OCCULT		INTRATHYROIDAL		EXTRATHYROIDAL		N	
	Papillary Follicular		Papillary Follicular		Papillary Follicular		Papillary Follicular	
	N=21	N=2	N=23	N=11	N=15	N=2	N=59	N=15
TOTAL								
THYROIDECTOMY n=22	5	2	8	2	4	1	17	5
LOBECTOMY n=43	10	0	12	9	11	1	33	10
RESECTIONS n=9	6	0	3	0	0	0	9	0

iodine uptake of more than 2% of the supplied dose. In addition, ^{131}I treatment was given postoperatively to four patients with distant metastases and to two with residual local cancer.

Outcome in patients treated for cure

At follow-up 2 to 20 years after diagnosis all patients except one could be traced. Twenty patients had died; autopsy was performed in 18 of these. The median observation time for the group of patients treated by total thyroidectomy was five years, for the group treated by lobectomy or thyroid resection 12 years.

None of the 78 patients, treated for cure, died from TC.

The various types of recurrence in the 74 patients treated for cure for papillary and follicular TC, are in table XI related to the primary surgical procedure. One woman, treated by lobectomy for papillary TC at the age of 15, was surgically treated for recurrence at the site of the thyroid gland eleven years later. This patient was alive without recurrence eight years after the second operation. Seven patients were surgically treated for lymph node metastases within four years of the primary surgical procedure. The distant metastases (table XI) were all diagnosed radiographically and were all situated in the lungs; in four of these cases the recurrences were diagnosed within five years after the operation, in the fifth case (uncertain) the recurrence was detected after nine years.

The four patients with medullary carcinoma were all free of recurrence at the follow-up.

Outcome in patients treated for palliation

The four patients treated for palliation by locally radical total thyroidectomy for follicular (three cases) or papillary (one case) cancer, were all alive and in good health three to nine years after the primary operation. The patients with follicular cancer had residual, slowly progressing

Table XI: Recurrence in 74 patients with papillary or follicular cancer considered to be operated for cure at the primary surgical procedure

TYPE OF RECURRENCE	Papillary n=59		Follicular n=15	
	Ttx ¹⁾ n=17	Ptx ²⁾ n=42	Ttx ¹⁾ n=6	Ptx ²⁾ n=9
Clinical recurrence in thyroid gland (surgically treated)	0	1	0	0
Node metastases (surgically treated)	2	2	1	2
Clinically diagnosed distant metastases	1	1 ³⁾	2	1 ⁴⁾
Incidental autopsy finding without clinical significance	0	2	0	0

1) Total thyroidectomy

2) Partial thyroidectomy

3) The recurrence uncertain

4) Dead with recurrence. TC not main cause of death.

metastases, while the patient with papillary TC was without demonstrable metastases. At the presentation he had bone metastases which disappeared after surgery and ¹³¹I treatment.

Of the eight patients in whom the operation was palliative due to local growth, four died from TC within six years of diagnosis, one died from a stroke with local residual TC after six years, and two were alive with advanced local disease three years after the operations. One patient died postoperatively from pulmonary embolism.

Complications to surgery

Postoperatively, two patients, 63 and 79 years old, died from pulmonary embolism. Non-intentional paralysis of one laryngeal recurrent nerve more than three months postoperatively was found in three patients amounting to three per cent of the operated lobes. Persistent hypocalcemia more than six months postoperatively was found in 1.1% (one case in the group treated by total thyroidectomy).

COMMENTS

The surgical treatment of TC often includes, besides procedures for the primary tumor, excision of lymph node metastases. In recent years most authors have agreed that excision of enlarged lymph nodes only rather than classical radical neck should be the method of choice, and is in most cases sufficient to prevent recurrence (36,37,90). The present study therefore focused on the surgical treatment of the primary tumor.

The surgery performed in Malmö was, particularly during the 1960s, relatively conservative compared with other Scandinavian series where total thyroidectomy was the dominating type of procedure (91,92). A direct comparison of the prognoses after total and partial thyroidectomy respectively, was not considered advisable since patients treated by total thyroidectomy were assumed to be burdened with a worse prognosis because total thyroidectomies were probably performed to a greater extent than partial thyroidectomies in patients with advanced tumors. In the present study the local recurrence rate in patients operated for cure was used as an indication of insufficient local surgical therapy.

One argument for total thyroidectomy in papillary cancer has been the reported high rate of microscopic foci in the opposite lobe in patients with grossly unilateral tumor (35). The frequency of such foci has been reported to be 30 to 80 per cent, partly dependent on the accuracy of the histopathologic examination (39,93). In the present study the rate of local recurrence of 2.4% of the patients treated by partial thyroidectomy for papillary cancer (table IX) does not seem to correspond to these high rates

of microscopic foci. The local recurrence rate was also lower than the corresponding rates reported by other authors (38,94). One explanation of this could be the relatively low frequency of irradiation to the neck in Malmö (section B 2), since this is reported to involve a high rate of bilateral papillary TC (95); in the present study the frequency of bilateral involvement, as described previously (section C), was 18% in glands routinely examined. Another explanation of the low recurrence rate in the present study could be that all our patients were treated with a suppressive dose of thyroxine since growth of TC is influenced by the TSH-level (96,97).

Total thyroidectomy is clearly justified in cases having papillary or follicular carcinoma with distant metastases. The reason for this is, that metastases from these tumors often concentrate iodine which makes it possible to use ^{131}I as a precise internal irradiation therapy. One condition for such a treatment is that normal thyroid tissue is ablated, since it has a higher capacity than metastases to concentrate iodine. The effectiveness of the method is well documented (98), and was supported in the present study where four patients were successfully treated in this manner.

Total thyroidectomy is also preferable if screening for metastases or residual differentiated TC using ^{131}I is desired, for the reasons given above. Whole-body scan was used in 21 patients in the present study but no previously unknown metastases were unveiled. According to other reports, cases of metastases from differentiated TC may be detected at an earlier stage by whole-body scan than by other methods (99,100). These findings could be one argument for total thyroidectomy if earlier diagnosis of distant metastases means improved survival or quality of life.

The most important arguments against total thyroidectomy are the risks of hypoparathyroidism and of bilateral recurrent nerve paralysis. Both of these complications are serious and considerably influence the quality of life in affected patients. The frequency of hypoparathyroidism reported in literature varies between 3 and 27% (101), whereas bilateral nerve paralysis seems to be infrequent (68,102). The postoperative complication rate can probably be reduced by careful surgical technique (101), and by implantation of

devascularized parathyroid tissue (103). However, the safest way to maintain normal parathyroid function and to preserve at least one nerve intact, should be to leave one thyroid lobe untouched, as is done in a lobectomy. The risk of postoperative complications has been shown to increase in patients who have a second operation (104). If the primary surgical procedure is always at least a lobectomy, the risks of postoperative complications at any second operation should not exceed the risks at the primary operation, because the tissue close to the nerve and to the parathyroids on the opposite side is unexplored.

Conclusions

Total thyroidectomy is the method of choice in the treatment of differentiated TC if the tumor involves the whole gland or if non-resectable metastases are present. Local recurrence after procedures less than total thyroidectomy seems to be infrequent, provided that thyroxine in a TSH-suppressive dose is given postoperatively. A conservative surgical approach is therefore considered indicated in most cases of localized papillary and follicular TC, thus reducing the risk of postoperative complications.

2 NON-SURGICAL TREATMENT (III, IV, V)

The non-surgical therapy consists of treatment given in addition to the surgical, as well as treatment of patients not surgically treated and of patients with recurrent disease after surgery. Additional therapy (to surgery) was considered in the former section; therefore the present section focuses on the other aspects of non-surgical therapy.

Only one of the twelve patients with anaplastic TC, clinically diagnosed, was surgically treated (table V). Six of the remaining eleven patients were treated with either external irradiation (two cases) or ^{131}I (one case) or with a combination of external irradiation and cytostatic drugs or ^{131}I (three cases). The prognosis was poor irrespective of treatment given: all patients died from TC within one year.

Three patients with a clinical diagnosis of differentiated TC were not surgically treated. Combined with thyroxine, both ^{131}I and external irradiation were given to two of these, and external irradiation alone to one patient. All three patients died from TC one to three years after diagnosis. It was impossible to estimate if the treatment was beneficial in any of the cases.

Three of five patients, who developed distant metastases after a primarily curative operation for TC (table XI), were treated with ^{131}I , since the metastases were shown to concentrate iodine. In two cases the metastases progressed only slowly after the institution of ^{131}I therapy. In the third patient the metastases progressed rapidly in spite of additional therapy with cytostatic drugs.

Two patients with differentiated TC primarily treated for cure, died from pulmonary fibrosis five and 20 years after presentation, respectively. The pulmonary fibrosis was in both cases considered a result of external irradiation therapy for recurrent nodes in the mediastinum.

COMMENTS

It is difficult to evaluate from the present study which treatment is best for patients with anaplastic TC, partly because only seven patients were treated, partly because the treatment given was non-uniform. Several attempts have been made to design a mode of treatment, of at least palliative value, for patients with this tumor (86,105). So far, these attempts have not been successful. The major efforts should therefore be concentrated on tracing and treating patients with differentiated TC early, for the purpose of eliminating tumors which might later become anaplastic.

The value of thyroxine and ^{131}I in the treatment of distant metastases from differentiated TC was considered in the former section.

Two patients in the present study died from late effects of external irradiation therapy. Treatment with ^{131}I for TC metastases has been

suggested to result in an increased incidence of leucemia (106). The favorable prognosis for most patients with differentiated TC should be taken into account when irradiation therapy (internal or external) is considered.

E. Survival

Thirty-four of the 104 patients with clinical TC (III) died during the follow-up period. The cause of death was based on autopsy records in 32 cases. The two remaining patients died from heart failure according to the death certificates; none of them had clinical signs of recurrence of TC.

1 SURVIVAL TIME IN FATAL CASES (V)

Since the survival time for patients who died from TC is of importance to decide the length of the follow-up of clinical materials, this subject was particularly studied in paper V, where all patients - known to have died from TC in Malmö during a period of 18 years - were included.

All patients with anaplastic TC (12 cases) died within one year of diagnosis. Six of nine patients with papillary TC died during the first five years, two died between five and ten years after the presentation. One patient with papillary TC died 20 years after diagnosis, not from the TC but from pulmonary fibrosis, probably caused by irradiation therapy. All patients with a clinical diagnosis of follicular TC (five cases) died within five years from their malignant disease. Two patients with a medullary carcinoma, which was part of a MEN syndrome, died 13 and 27 years after the TC diagnosis.

COMMENTS

The survival times for fatal cases of differentiated TC in the present study were relatively short compared with those of other series (40,107); only two patients died from papillary TC five years or more after the diagnosis. According to a report by Tollefsen et al on fatal cases of papillary TC (40), 27% of the patients died more than ten years after diagnosis. In that study, the cause of death was, however, verified by autopsy in only 11%. Causes of death based on autopsy records are, of course, always more reliable than clinically based diagnoses, but this is particularly true for a slow-growing tumor like differentiated TC. In the present study of clinical TC (III), five of 34 deaths were proven to be caused by

metastases from neoplasms other than TC. However, the discrepancy in the proportion of late deaths between the present and other studies can probably not be explained by a difference in autopsy documentation alone. Other factors like patient selection, differences in the natural history of TC, collection of patients during different time periods, and differences in treatment, may also be of importance.

It is concluded that deaths from papillary, follicular, and anaplastic TC in the Malmö material occurred most frequently during the first five years of observation, and that a survival time of ten years or more was infrequent if the disease was fatal.

2 SURVIVAL FOR ALL PATIENTS WITH THYROID CARCINOMA (III)

The outcome, as found at follow-up 2 to 20 years after diagnosis, is shown in table XII. The observed and expected survival rates for all 104 patients are shown in figure 3. The distance between the curves does not increase after the seventh year of observation, indicating that the survival in the patient group after this point is not below that expected for an average group of individuals in Malmö with the same age and sex distribution, but without TC.

COMMENTS

The survival for a group of patients with TC is, of course, dependent on the distribution of the tumors by histologic type and by tumor stage. Thus, the survival for patients with TC clinically diagnosed in Malmö during the 1970s can be expected to be better than the prognosis for patients from the 1960s due to the higher proportion of intrathyroidal tumors in the former group of patients (see section C). A comparison of the survival rates between the periods is, however, not considered advisable, because it would be biased by too short a follow-up time of the latest entries in the study.

Table XII: Results at the follow-up, December 31, 1979, in 104 patients with clinical TC diagnosed in Malmö 1960 - 1977.

	Papillary n = 66	Follicular n = 22	Medullary n = 4	Anaplastic n = 12	Total n = 104
Alive without recurrence	49	10	3	0	62
Dead without recurrence	7	3	1	0	11 ¹⁾
Alive with recurrence	3	5	0	0	8
Dead from other cause with TC recurrence	4	1	0	0	5
Death caused by TC	3 (5%)	3 (14%)	0 (0%)	12 (100%)	18 (17%)

1) Two patients not autopsied

There are only a few studies dealing with the prognosis of all TC, based on demographically defined populations. The prognosis in a Finnish population, as described by Franssila (20) was considerably worse than that found by us in the Malmö area. Probably this is mainly due to a higher proportion of anaplastic TC and of tumors with extrathyroidal growth in the Finnish material. The crude mortality rate from TC of 17% in our study (table XII) was close to that of 15% found in the population of Olmstedt county, Minnesota (108). Also, the distribution of the tumors by histologic type and the proportion of occult carcinoma were similar in the two patient materials.

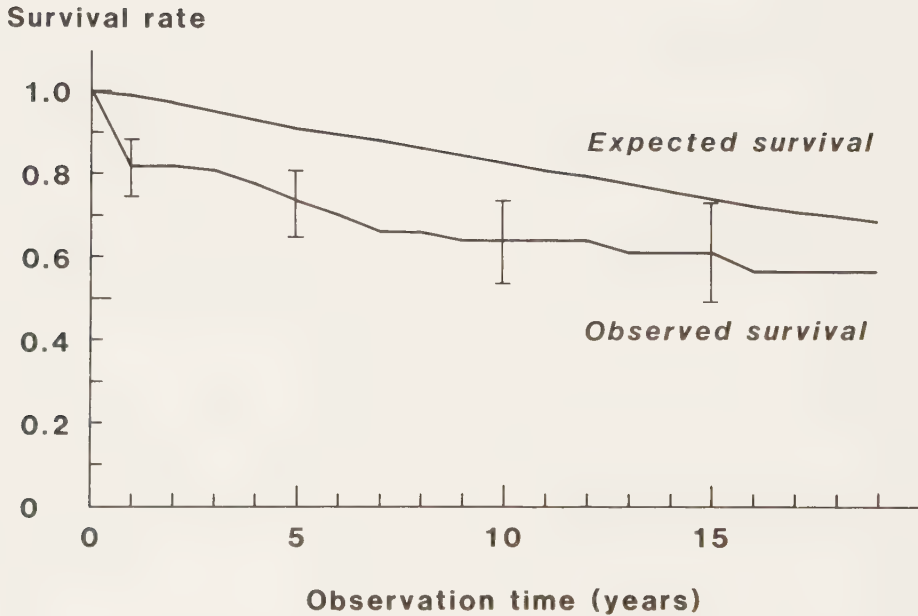


Fig 3: Cumulated survival rate with 95% confidence limits in 104 patients with TC related to expected survival rate for a corresponding group of individuals.

3 SURVIVAL BY HISTOLOGIC TYPE (III, V)

The outcome for patients with the different histologic types of TC is shown in table XII. The prognosis was worst among patients with anaplastic TC followed by follicular and papillary TC (fig 4). All patients with anaplastic TC died within one year. The survival rate was significantly lower than expected, both for patients with papillary TC and for patients with follicular TC after five and one year of observation, respectively ($p < 0.05$). None of the four patients with medullary TC, clinically diagnosed between 1960 and 1977, died from TC. In the autopsy study (V), however, four cases of fatal, medullary TC were identified (table V).

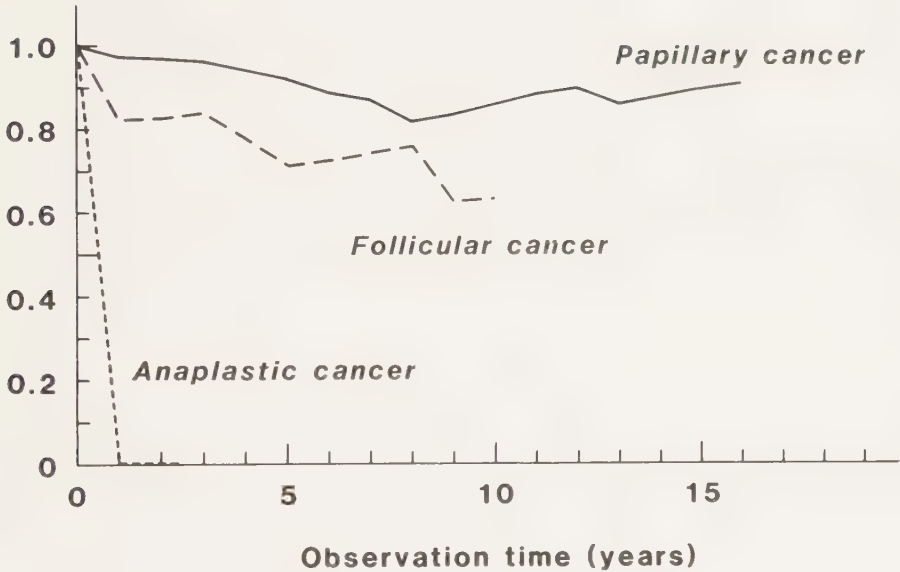
Survival rate

Fig 4: Relative survival rate for patients with papillary TC (n=66), follicular TC (n=22), and anaplastic TC (n=12).

COMMENTS

The significance of the histologic type for the survival of patients with TC, as found in the present study, is in good agreement with other reports (20,25). The survival for patients with medullary TC could not be evaluated because the number of such cases was too small. The prognosis in these cases seems, according to literature, to be worse than that for papillary and follicular TC but better than that for anaplastic TC (109,110).

It was previously suggested that the detection rate of TC in the population affects the distribution of the tumors by histologic type (section C). The prognosis of clinically diagnosed TC may also be influenced by the detec-

tion rate, partly for the same reasons. Advanced tumors with serious symptoms such as air-way obstruction or metastases, are more likely to be diagnosed than indolent tumors where a lump in the neck is the only symptom. The detection rate should, above all, influence the prognosis of papillary TC, since indolent tumors are most frequent in this group. These factors may in part explain why patients with papillary TC in the Malmö area had a considerably better prognosis than found by Franssila (20) and Lindahl (111) in a Finnish and a Danish population, respectively. The incidence of papillary TC in the Finnish population studied, can be calculated to 0.38 (table VIII) corresponding to 1.5 in Malmö. In the Danish study no incidence figure was available, but papillary cancer constituted only approximately 25% of all TC, and the incidence of all TC in Denmark was reported to be comparatively low.

Anaplastic TC was invariably fatal in the present study. According to other reports, occasional patients with anaplastic TC have been treated for cure and have survived for several years free from disease (20,112). Such patients have, however, mostly had carcinoma of the small cell type, which were excluded from the present study because this type was regarded as malignant lymphoma. Reports on long-term survival for patients with a diagnosis of giant or spindle cell carcinoma are uncommon.

4 SURVIVAL BY TUMOR STAGE (III)

The survival rates for patients with occult (n=23) and intrathyroidal (n=23) papillary TC were not statistically different from the expected rate (fig 5). One patient with incurable occult TC (due to mediastinal node metastases) died from TC four years after presentation. No patient with intrathyroidal tumor died from TC. The survival rate for the 20 patients with extrathyroidal papillary tumors was significantly lower than expected after the fifth year of observation (fig 5). Two patients died postoperatively from pulmonary embolism and two died three and six years after diagnosis, from TC.

The number of patients with follicular TC of different stages was too

Survival rate

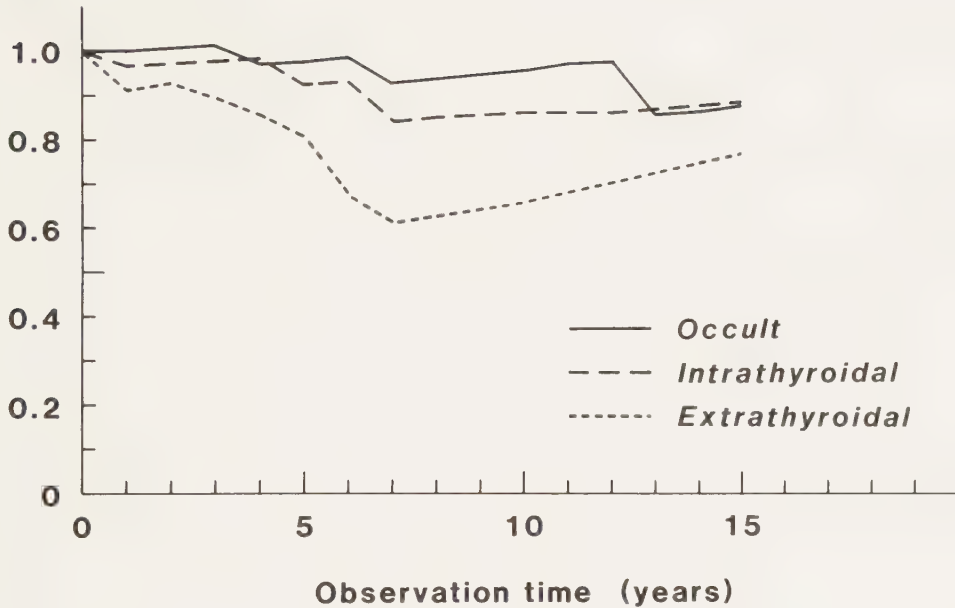


Fig 5: Relative survival rate for patients with occult (n=23), intra-thyroidal (n=23) and extrathyroidal (n=20) papillary TC.

small for evaluation according to the life table method (table VII). The trend in survival was, however, the same as in the papillary group: none of the patients with occult (n=1), or intrathyroidal (n=14) tumors died from TC, whereas three of seven patients with extrathyroidal growth died from their malignant thyroid disease.

One of five patients (with a follicular extrathyroidal tumor) with papillary or follicular TC and distant metastases at presentation (table VII) died within one year from TC. The other four patients were all alive at follow-up three to nine years after diagnosis.

COMMENTS

The present findings confirm the validity of using the local extension of differentiated TC in the classification into tumor stages: patients with extrathyroidal tumors had a considerably worse prognosis than those with intrathyroidal tumors.

The term occult TC (which means TC concealed from observation) was originally introduced when it became obvious that the prevalence of small thyroid carcinomas, particularly of the papillary type, was very high, as indicated by autopsy studies (4,6,29,56). These small tumors become clinically important when they are incidentally unveiled at neck operations done for another purpose. Such cases probably have a very favorable prognosis. The present definition of occult (see Definitions), however, seems to be inappropriate, partly because approximately 50% of these tumors (or their metastases) were observed preoperatively (and thus not concealed), partly because patients with a primary diagnosis of occult TC actually died from their malignant disease (table VII). From a clinical and prognostic point of view, it therefore seems justified to consider those occult papillary carcinomas, not larger than 1.5 cm in diameter which are discovered incidentally, as a separate group and to include the remaining clinically discovered occult carcinomas within the groups of intrathyroidal and extrathyroidal carcinomas. Since the number of incidentally discovered follicular and medullary carcinomas is small, it is difficult to estimate the prognosis for these groups. It seems reasonable to manage such cases in the same way as clinically diagnosed carcinomas, until further information is available.

5 SURVIVAL BY NODE STATUS (III)

Within the papillary group, patients with extrathyroidal tumors had a significantly higher frequency of node metastases than patients with intrathyroidal and occult tumors (table VII, $p < 0.01$). The node status did not affect the survival significantly in the whole group of patients with papillary TC (fig 6). Two patients with follicular TC had node metastases at the presentation (table VII). In both cases the node metastases were

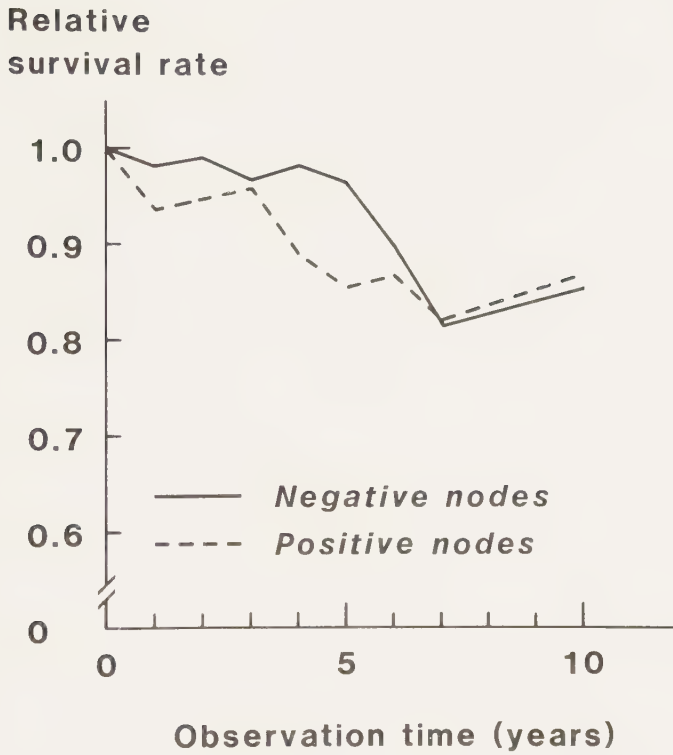


Fig 6: Relative survival rate in patients with papillary TC with (n=29) and without (n=37) lymph node metastases.

part in an advanced disease, and both patients died from TC.

COMMENTS

The significance of node metastases for the survival of patients with papillary TC has been widely discussed in the literature. Most authors believe that the node status is of little importance for the prognostic prediction (20,28). It has even been claimed that node metastases have a protective effect, in that patients with positive nodes have a higher survival rate than those without nodes (107). Harwood et al found that the presence of node metastases actually had an adverse effect upon survivorship after adjustment for age (113). In Harwood's material the rate of cases with positive nodes was higher in younger than in older patients. Since young age at diagnosis is associated with improved survival, it was suggested that conflicting results in other studies could be ascribed to lack of adjustment for age in these studies. This suggestion was not supported by the present study; the frequency of cases with positive nodes was not found to be dependent on the age of the patients. It was, on the other hand, obvious in our study, contrary to others (25,26), that the occurrence of node metastases in papillary TC was strongly correlated with the local behavior of the primary tumor: 75% of patients with extrathyroidal tumors had positive nodes, whereas the corresponding frequency in patients with occult and intrathyroidal tumors was 30%. Accordingly, it might be expected that patients with positive nodes have a worse prognosis than those without nodes (due to the adverse prognostic potential of extrathyroidal growths). Since this was not the fact, the suggestion may be made that node metastases in our patients had rather a slightly favorable than a negative effect on survival. The two patients belonging to the group of patients with extrathyroidal tumors who died from TC (section E 3), actually had no node metastases at presentation.

6 SURVIVAL BY AGE (III)

Patients below the age of 40 with papillary TC had a significantly higher survival rate than those aged 40 or more, five years after diagnosis (fig 7). None of the 25 young patients died from TC, neither did any of the three patients with follicular TC aged below 40 at presentation.

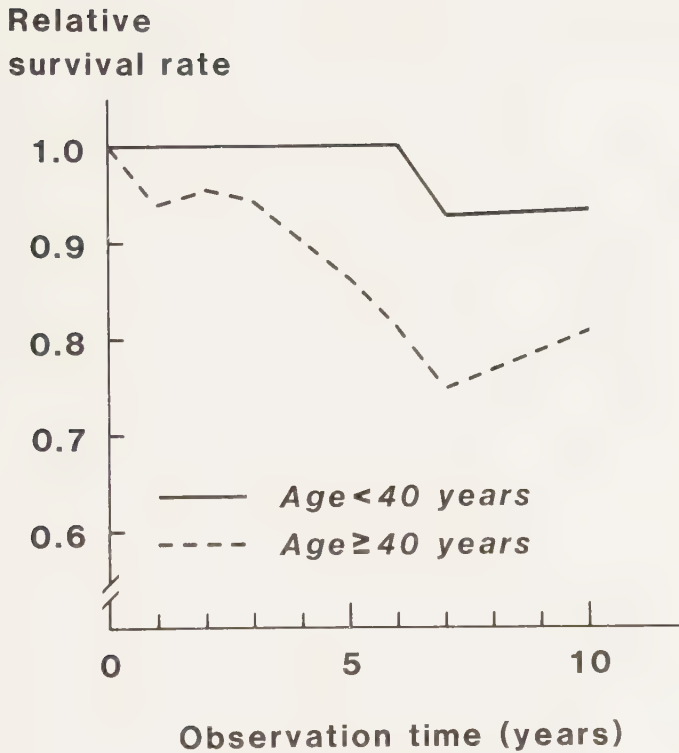


Fig 7: Relative survival rate in patients with papillary TC. Patients below the age of 40 ($n=25$) compared with patients aged 40 or more ($n=41$).

COMMENTS

It is a general observation that young age at diagnosis is usually associated with a good prognosis (30,60). It has, however, been suggested that this is in part erroneous, since patients who are young at diagnosis may

die from a slow-growing TC decades after presentation (84). In the present study there was no support for such a hypothesis. Only two of 38 patients in whom the TC was fatal (V) were below the age of 40 at diagnosis (cf fig 2). One of these had medullary TC; the other one died from late effects of irradiation therapy 20 years after the diagnosis of papillary TC. Also the difference in mean age at diagnosis of patients with clinical TC and of patients in whom the disease was fatal (table VI), stresses the importance of age at diagnosis as a prognostic factor in patients with differentiated TC.

Franssila pointed out that age is linked to histologic type and stage of tumor, and he stated that age is not of great importance in the final post-operative estimation of the prognosis if patient-materials are adjusted for histologic type and tumor stage (20). This statement was supported in our study as far as histologic type is concerned: all patients with anaplastic TC were above the age of 40; only three of 22 patients with follicular TC were below the age of 40 at presentation. We do not, however, agree with Franssila to the same extent concerning the statement on tumor stage. The mean age of patients with extrathyroidal papillary tumors was certainly eleven years higher than that for patients with occult and intrathyroidal tumors. There were, however, five patients (25%) with extrathyroidal tumors aged below 40 at diagnosis; none of them died from TC, nor did any of them have recurrence. This is in contrast to the survival of the whole group of patients with extrathyroidal papillary tumors (fig 5) and supports the significance of age for the outcome.

7 SURVIVAL BY SEX (III, V)

The relative survival rate for men and women, respectively, is illustrated in fig 8 a for patients with all types of TC, and in fig 8 b for those with differentiated TC. The difference in survival between the sexes is not significant at any point. The distance between the curves is greater in fig 8 a than in fig 8 b, which reflects the fact that the ratio between men and women in the group with anaplastic TC (where all patients died) was 1:2, whereas the rate was 1:3 in the group with differentiated TC.

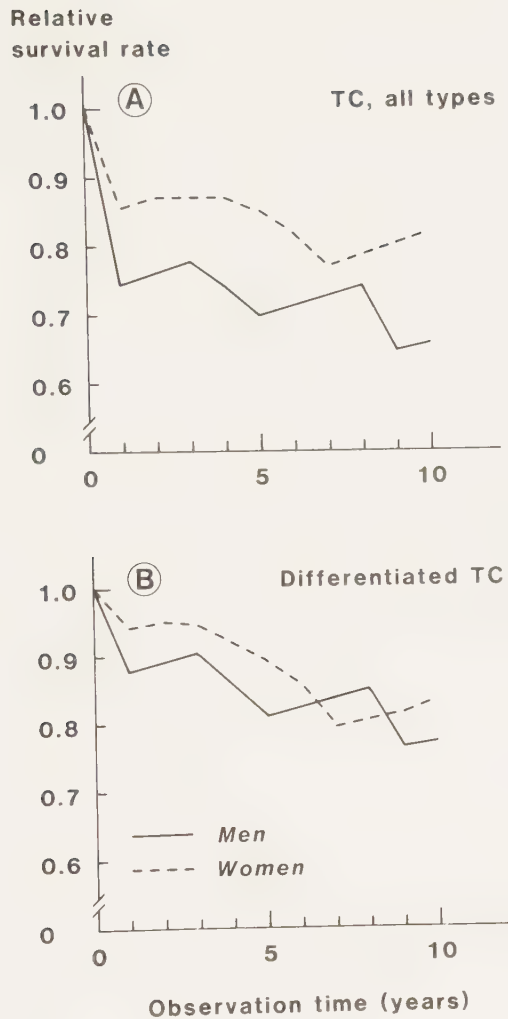


Fig 8: Relative survival rate by sex of 104 patients with all histologic types of TC (A), and of 92 patients with differentiated TC (B).

The male/female ratio in the 38 patients who died from TC (V) was 1:1.4. The ratio was practically the same for the different histologic types. It was not significantly different from the sex ratio of 1:2.9 in patients with clinical TC.

COMMENTS

The difference in survivorship between the sexes was close to be significant and the results in our study are not in conflict with statements by other authors that the male sex is an unfavorable prognostic factor (20, 107). It has been suggested that this is mainly due to a proportionally higher frequency of males among patients with anaplastic TC (84). This was in part supported in our study (cf fig 8A & B). The male/female ratio for patients in whom differentiated TC was fatal, was, however, also higher than the corresponding ratio for patients with a clinical diagnosis of TC. One explanation of this might be that women are more likely than men to have surgery for benign neck disorders such as nodular goiter, thyrotoxicosis, and hyperparathyroidism, and with this, an increased possibility of having an incidental occult TC detected. This would implicate a better prognosis for the whole group of women with differentiated TC since patients with incidentally discovered tumors have good prognosis. In fact, all 13 incidentally discovered occult tumors in the present study (section C) were diagnosed in women.

General summary and conclusions

The annual incidence of clinically diagnosed TC in Malmö was, on an average, 2.4/100,000 during the years 1960 to 1977. This was 1.2 lower than the corresponding incidence in whole Sweden as reported by the National Cancer Registry. The main reason for the difference was suggested to be inclusion in the official figures of autopsy cases and of cases with benign diagnosis rather than a true difference in the prevalence of TC. During the later part of the study an increase in the incidence of differentiated TC of approximately 70% was noted. This was considered to be due to increased health awareness and availability of medical care because only the number of tumors with less advanced growth increased.

The average annual mortality rate from TC in Malmö was 0.9/100,000 which was 0.4 lower than the corresponding official rate in all Sweden. The difference was suggested mainly to be due to inclusion in the official figures of cases not dying from TC. The mortality rate did not change significantly during the period of investigation.

The prevalence of palpable thyroid lesions in 477 middle-aged women was found to be 11.3%, and of a solitary thyroid nodule, 6.5%. All goiters (n=54) were considered to be benign after evaluation with thyroid scan, fine-needle aspiration biopsy cytology and, in one case, histopathologic examination following surgery. It was concluded that goiter is a common disorder among women living in non-endemic areas, and that most goiter, including palpable solitary nodules, can be classified after evaluation as multinodular goiter.

The malignant diagnosis was clinically obvious or strongly suspected (rapidly growing goiter or metastases) in about one quarter of all patients (n=104) with clinical TC in Malmö 1960 to 1977, whereas a solitary thyroid nodule was the only sign in 60%. Anamnestic data and physical examination were of limited value in the evaluation of patients with this sign. Fine-needle aspiration biopsy cytology was considered the best single method in predicting or ruling out malignancy in solitary nodules. The final histopathologic diagnosis was malignant in 40% of nodules with a

cytologic diagnosis (CD) of malignancy or neoplasia; of the remaining cases with such a CD, 50% had a final diagnosis of follicular adenoma, and 10% of colloid goiter. The accuracy of a benign CD (colloid goiter or thyroiditis) was high provided the cytologic sample was representative of the underlying pathologic change. A thyroid scan showing that a palpable solitary nodule was either part of a multinodular goiter or "hot", supported a benign diagnosis. Considerably elevated serum thyroglobulin values in patients with solitary nodules but without thyrotoxicosis were found to support a malignant diagnosis.

Seventy-eight of 90 surgically treated patients were considered to be operated for cure. In 52 of these (67%) the surgical procedure was less than total thyroidectomy. None of the patients treated for cure had died from TC at the follow-up two to 20 years after surgery. One patient treated with lobectomy for papillary cancer had a local recurrence which was excised successfully. No further patient treated for cure had local recurrence. It was concluded, that local recurrence after procedures less than total thyroidectomy considered to be curative are uncommon provided that thyroxine is given postoperatively. A conservative approach in most cases of localized TC was considered indicated, thus reducing the risk of postoperative complications.

The percentage distribution by histologic type of tumors clinically diagnosed (n=104) was: papillary cancer 65%, follicular 21%, medullary 4% and anaplastic 12%. The prognosis as estimated by the life table method was worst for patients with anaplastic TC followed by follicular, papillary and medullary. The validity of using the relationship of the tumor to the thyroid capsule (*i.e.* intrathyroidal and extrathyroidal growth) as a basis for classification into tumor stages was supported in the present study: the mortality in patients with intrathyroidal tumors was lower than in those with extrathyroidal tumors. The definition of occult TC, *i.e.* a TC not larger than 1.5 cm without regard to the relation to the thyroid capsule, was considered inappropriate and a change in the conception of occult TC was proposed. The presence or absence of node metastases in TC did not seem to have major significance for the prognosis.

The significance of age for survival was strongly supported here. Deaths from TC clinically diagnosed before the age of 60 were infrequent, whereas the disease after this age increasingly often was fatal. This was partly due to a late onset of anaplastic TC, partly to a higher mortality in older than in younger patients with papillary or follicular TC. The prognosis was somewhat worse in men than in women, mainly caused by the fact that the male/female ratio was higher in the group of patients with anaplastic TC (where all died) than in all patients with TC.

The survival time in patients with TC, in whom the disease was fatal, was particularly studied in an autopsy series composed by all 38 patients known to have died from TC in Malmö during an 18-year period. All patients with anaplastic TC died within one year from diagnosis, whereas the majority of patients with papillary or follicular TC (in whom the TC was fatal) died within five years; one patient with papillary and two with medullary TC survived more than ten years.

References

1. Sancho-Garnier H. L'épidémiologie des cancers de la thyroïde. *Ann Radiol* 20:715, 1977.
2. Schottenfeld D, Gershman ST. Epidemiology of thyroid cancer. *CA-A Cancer Journal for Clinicians* 28:66, 1978.
3. Aldersson MR. Thyroid cancer: epidemiology. *Recent Results Cancer Res* 73:1, 1980.
4. Sampson RJ, Woolner LB, Bahn RC, Kurland LT. Occult thyroid carcinoma in Olmstedt county, Minnesota: prevalence at autopsy compared with that in Hiroshima and Nagasaki, Japan. *Cancer* 34:2072, 1974.
5. Fukunaga FH, Lockett LJ. Thyroid carcinoma in the Japanese in Hawaii. *Arch Pathol* 92:6, 1971.
6. Bondeson L, Ljungberg O. Occult thyroid carcinoma at autopsy in Malmö, Sweden. *Cancer* 47:319, 1981.
7. Maruchi N, Furihata R, Makiuchi M. Population surveys on the prevalence of thyroid cancer in a non-endemic region, Nagano, Japan. *Int J Cancer* 7:575, 1971.
8. Gogas JG, Katsikas D, Sechas M, Kakaviatos N, Skalkas GD. Prediction of malignancy in solitary thyroid nodules in a country with endemic goiter. *Am J Surg* 132:623, 1976.
9. Hoffman GL, Thompson NW, Heffron C. The solitary thyroid nodule. A re-assessment. *Arch Surg* 105:379, 1972.
10. Kelly FC, Snedden WW. Prevalence and geographic distribution of endemic goitre. In: *Endemic goitre. WHO monograph 44*. Geneva: World Health Organization, pp 27, 1960
11. Söderström N. Aspiration-biopsy puncture of goiters for aspiration biopsy. *Acta Med Scand* 144:237, 1952.
12. Einhorn J, Franzén S. Thin-needle biopsy in the diagnosis of thyroid disease. *Acta Radiol* 58:321, 1962.
13. Löwhagen T, Granberg PO, Lundell G, Skinnari P, Sundblad R, Willems JS. Aspiration biopsy cytology (ABC) in nodules of the thyroid suspected to be malignant. *Surg Clin North Am* 59:3, 1979.
14. Walfish PG, Hazani E, Strawbridge HTG, Miskin M, Rosen IB. Combined ultrasound and needle aspiration cytology in the assessment and management of hypofunctioning thyroid nodule. *Ann Int Med* 87:270, 1977.

15. Ann Int Med, Editorial: Managing the solitary thyroid nodule: Role of needle biopsy. Ann Int Med 87:375, 1977.
16. Hamberger B, Gharib H, Melton LJ, Goellner JR, Zinsmeister AR. Fine-needle aspiration biopsy of thyroid nodules. Impact on thyroid practice and cost of care. Am J Med 73:381, 1982.
17. Rosen IB, Wallace C, Strawbridge HG, Walfish PG. Reevaluation of needle aspiration cytology in detection of thyroid cancer. Surgery 90:747, 1981.
18. Meissner WA, Warren S. Tumors of the thyroid gland. In: Atlas of tumor pathology. 2nd series, Armed Forces Institute of Pathology, Washington DC, 1969.
19. Hedinger C, Sobin LH et al. Histological typing of thyroid tumours. International histological classification of tumours, No 11. Geneva: WHO, pp 17, 1974.
20. Franssila KO. Prognosis in thyroid carcinoma. Cancer 36:1138, 1975.
21. Frazell EL, Duffy BJ. Hürtle cell cancer of the thyroid. Cancer 4:952, 1951.
22. Tollefsen HR, Shah JP, Huvos AG. Hürtle cell carcinoma of the thyroid. Am J Surg 130:390, 1975.
23. Bondeson L, Bondeson AG, Ljungberg O, Tibblin S. Oxyphile tumors of the thyroid. Follow-up of 42 surgical cases. Ann Surg 194:677, 1981.
24. Thomas CG, Buckwalter JA. Poorly differentiated neoplasms of the thyroid gland. Ann Surg 177:632, 1973.
25. Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR. Classification and prognosis of thyroid carcinoma. A study of 885 cases observed in a thirty year period. Am J Surg 102:354, 1961.
26. Beaugié JM, Brown CL, Doniach I, Richardson JE. Primary malignant tumors of the thyroid: the relationship between histological classification and clinical behavior. Br J Surg 63:173, 1976.
27. Iida F, Yonekura M, Miyakawa M. Study of intraglandular dissemination of thyroid cancer. Cancer 24:764, 1969.
28. Hirabayashi RN, Lindsay S. Carcinoma of the thyroid gland. A statistical study of 390 patients. J Clin Endocrinol Metab 21:1596, 1961.
29. Fukunaga FH, Yatani R. Geographic pathology of occult thyroid carcinomas. Cancer 36:1095, 1975.

30. Fraumeni CM, Patchefsky AS, Cobanoglu A. Thyroid carcinoma. A clinical and pathological study of 125 cases. *Cancer* 43:2414, 1979.
31. Patchefsky AS, Keller IB, Mansfield CM. Solitary vertebral column metastases from occult sclerosing carcinoma of the thyroid gland: Report of a case. *Am J Clin Pathol* 53:596, 1970.
32. Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP. Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine* 56:171, 1977.
33. Staunton MD, Greening WP. Treatment of thyroid cancer in 293 patients. *Br J Surg* 63:253, 1976.
34. Saxén E, Franssila K, Bjarnasson O, Normann T, Ringertz N. Observer variation in histologic diagnosis of thyroid cancer. *Acta Path Microbiol Scand* 86:483, 1978.
35. Clark RL, Ibanez ML, White EC. What constitutes an adequate operation for carcinoma of the thyroid. *Arch Surg* 92:23, 1966.
36. Block MA. Management of carcinoma of the thyroid. *Ann Surg* 185:133, 1977.
37. Cady B. Surgery of thyroid cancer. *World J Surg* 5:3, 1981.
38. Tollefsen HR, Shah JP, Huwos AG. Papillary carcinoma of the thyroid. Recurrence in the thyroid gland after initial surgical treatment. *Am J Surg* 124:468, 1972.
39. Russel WO, Ibanez ML, Clark RL, White EC. Thyroid carcinoma. Classification, intraglandular dissemination, and clinicopathological study based upon whole organ sections of 80 glands. *Cancer* 16:1425, 1963.
40. Tollefsen HR, DeGosse JJ, Hutter RVP. Papillary carcinoma of the thyroid. A clinical and pathological study of 70 fatal cases. *Cancer* 17:1035, 1964.
41. Höjer JA. Kropfstudien. *Svenska Läkarselskapets handlingar* 57:1, 1931.
42. Thorell JI, Larson SM. Radioimmunoassay and related techniques: Methodology and clinical applications. St Louis: CV Mosby, 1978.
43. Van Herle AJ, Uller RP, Matthews NL, Brown J. Radioimmunoassay for measurement of thyroglobulin in human serum. *J Clin Invest* 52:1320, 1973.
44. Cox DR. Some simple approximate tests for Poisson variates. *Biometrika* 40:354, 1953.
45. Berkson J, Gage RP. Calculation of survival rates for cancer. *Proc Mayo Clin* 25:270, 1950.

46. Ederer F, Axtell LM, Cuttler SJ. The relative survival rate: A statistical methodology. National Cancer Inst. Monographs, 6:101, 1961.
47. Colton T, Scd. Statistics in Medicine. Boston: Little Brown & Co, p 249, 1974.
48. Dingle PR, Ferguson A, Horn DB, Tubmen J, Hall R. The incidence of thyroglobulin antibodies and thyroid enlargement in a general practice in north-east England. Clin Exp Immunol 1:277, 1966.
49. Berge T, Ekelund G, Mellner C, Pihl B, Wenckert A. Carcinoma of the colon and rectum in a defined population. Acta Chir Scand Suppl 438, 1973.
50. Ekelund G. On colorectal polyps and carcinoma with special reference to their interrelationship. Thesis. Malmö General Hospital, Malmö 1974.
51. Lannerstad O. Död och sjukdom bland medelålders män. Thesis. Malmö General Hospital, Malmö 1978.
52. Lindhagen T. Crohn's disease in a defined population. Results of surgical treatment. Thesis. Malmö General Hospital, Malmö 1982.
53. Heise H. The effect of a temporary change in survival on the life table method for computing survival rates. Methodological note No 8, End results, Evaluation section, National Cancer Institute, February 1959.
54. Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Grimley Evans J, Young E, Bird T, Smith TA. The spectrum of thyroid disease in a community: The Whickham survey. Clin Endocrin 7:481, 1977.
55. Vander JB, Gaston EA, Dawber TR. Significance of solitary nontoxic thyroid nodules: Preliminary report. N Engl J Med 251:970, 1954.
56. Sampson R, Key CR, Buncher CR, Iijima S. Thyroid carcinoma in Hiroshima and Nagasaki. I. Prevalence of thyroid carcinoma at autopsy. JAMA 209: 65, 1969.
57. Cancer incidence in Sweden 1977. National Board of Health and Welfare. The Cancer Registry, Stockholm 1981.
58. Franssila KO, Saxén E, Teppo L, Bjarnasson O, Tullinius H, Normann T, Ringertz N. Incidence of different morphological types of TC in the nordic countries. Acta Path Microbiol Scand 89:49, 1981.
59. Causes of Death 1960-1977. Official statistics of Sweden. National Central Bureau of Statistics. Stockholm 1960-1977.

60. McKenzie AD. The natural history of thyroid cancer. A report of 102 cases analysed 10 to 15 years after diagnosis. *Arch Surg* 102:274, 1971.
61. Steiner AL, Goodman AD, Powers SR. Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: multiple endocrine neoplasia, type 2. *Medicine* 47:371, 1968.
62. Ljungberg O. On medullary carcinoma of the thyroid. *Acta Path Microbiol Scand Section A, Suppl* 231:1, 1972.
63. Lote K, Anderssen K, Nordal E, Brenhøvd IO. Familial occurrence of papillary thyroid carcinoma. *Cancer* 46:1291, 1980.
64. Phade VR, Lawrence WR, Max MH. Familial papillary carcinoma of the thyroid. *Arch Surg* 116:836, 1981.
65. Kitchin FD, Weinstein IB. Genetic factors in thyroid disease. In: Werner SC, Ingbar SH (eds). *The Thyroid*. 4th ed, New York, Harper & Row, p 495, 1978.
66. Refetoff S, Harrison J, Karanfilski BT, Kaplan EL, DeGroot LJ, Berman C. Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. *N Engl J Med* 292:171, 1975.
67. Pottner LM, Stone BJ, Day NE, Pickle LW, Fraumeni Jr JF. Thyroid cancer in Connecticut 1935-1975: An analysis by cell type. *Am J Epidemiol* 112:764, 1980.
68. Clark OH. Total thyroidectomy. The treatment of choice for patients with differentiated thyroid cancer. *Ann Surg* 196:361, 1982.
69. Blum M, Rothschild M. Improved nonoperative diagnosis of the solitary "cold" thyroid nodule. Surgical selection based on risk factors and three months of suppression. *JAMA* 243:242, 1980.
70. Ashcraft MW, Van Herle AJ. Management of thyroid nodules. II: Scanning techniques, thyroid suppressive therapy, and fine needle aspiration. *Head and Neck Surgery* 3:297, 1981.
71. Haugen SE, Sörli DG, Saebö-Larssen J, Sundsfjord JA. To the management of the solitary thyroid nodule. *Acta Chir Scand* 147:193, 1981.
72. Messaris G, Kyriakou K, Vasilopoulos P, Tountas C. The single thyroid nodule and carcinoma. *Br J Surg* 61:943, 1974.
73. Johnson PM. Thyroid and whole-body scanning. In: Werner SC, Ingbar SH (eds). *The Thyroid*. 4th ed, New York, Harper & Row, p 304, 1978.

74. Lang W, Georgii A, Stauch G, Kienzle E. The differentiation of atypical adenomas and encapsulated follicular carcinomas in the thyroid gland. *Virchows Arch (Pathol Anat)* 385:125, 1980.
75. LoGerfo P, Colacchio T, Caushaj F, Weber C, Feind C. Comparison of fine-needle and coarse-needle biopsies in evaluating thyroid nodules. *Surgery* 92:835, 1982.
76. Roitt IM, Torrigiani G. Identification and estimation of undegraded thyroglobulin in human serum. *Endocrinology* 81:421, 1967.
77. Pezzino V, Vigneri R, Squatrito S, Filetti S, Camus M, Polosa P. Increased serum thyroglobulin levels in patients with nontoxic goiter. *J Clin Endocrinol Metab* 46:653, 1978.
78. Pacini F, Pinchera A, Giani C, Grasso L, Doveri F, Baschieri L. Serum thyroglobulin in thyroid carcinoma and other thyroid disorders. *J Endocrinol Invest* 3:283, 1980.
79. Van Herle A, Uller RP. Elevated serum thyroglobulin. A marker of metastases in differentiated thyroid carcinomas. *J Clin Invest* 56:272, 1975.
80. Feldt-Rasmussen U, Beck K, Date J. Serum thyroglobulin in patients with toxic and non-toxic goitres compared to sex- and age-matched control subjects. *Acta Endocrinol* 91:264, 1979.
81. Colacchio TA, LoGerfo P, Colacchio DA, Feind C. Radioiodine total body scan versus serum thyroglobulin levels in follow-up of patients with thyroid cancer. *Surgery* 91:42, 1982.
82. Barsano CP, Skosey C, DeGroot LJ, Refetoff S. Serum thyroglobulin in the management of patients with thyroid cancer. *Arch Intern Med* 142:763, 1982.
83. Schneider AB, Favus MJ, Stachura ME, Arnold JE, Ryo UY, Pinsky S, Colman M, Arnold MJ, Frohman LA. Plasma thyroglobulin in detecting thyroid carcinoma after childhood head and neck irradiation. *Ann Int Med* 34:29, 1977.
84. Silverberg SG, Hutter RVP, Foote FW. Fatal carcinoma of the thyroid: histology, metastases, and causes of death. *Cancer* 25:792, 1970.
85. Ibanez ML, Russel WO, Albores-Savedra J, Lampertico P, White EC, LeeClark R. Thyroid carcinoma - biologic behavior and mortality. Postmortem findings in 42 cases, including 27 in which the disease was fatal. *Cancer* 19:1039, 1966.

86. Aldinger KA, Samaan NA, Ibanez M, Hill CS. Anaplastic carcinoma of the thyroid: A review of 84 cases of spindle and giant cell carcinoma of the thyroid. *Cancer* 41:2267, 1978.
87. Wahner HW, Cuello C, Correa P, Uribe LF, Gaitan E. Thyroid carcinoma in an endemic goiter area, Cali, Colombia. *Am J Med* 40:58, 1966.
88. Williams ED, Path MRC, Doniach I, Path FRC, Bjarnasson O, Michie W. Thyroid cancer in an iodine rich area. A histopathological study. *Cancer* 39:215, 1977.
89. Heitz P, Moser H, Staub JJ. Thyroid cancer. A study of 573 thyroid tumors and 161 autopsy cases observed over a thirty-year period. *Cancer* 37:2329, 1976.
90. Crile G Jr. The fallacy of the conventional radical neck dissection for papillary carcinoma of the thyroid. *Ann Surg* 145:317, 1957.
91. Sørheide O, Varhaug JE, Heiman P. Thyroid carcinoma: Diagnosis and treatment in 106 patients. *Acta Chir Scand* 145:137, 1979.
92. Grimelius L, Johansson H, Nilsson F, Wicklund H, Åkerström G. Thyroid carcinoma. Presentation of a clinical material with special aspects on the classification and operative treatment. *Uppsala J Med Sci* 83:35, 1978.
93. Clark RL, White EC, Russel WO. Total thyroidectomy for cancer of the thyroid: Significance of intraglandular dissemination. *Ann Surg* 149: 858, 1959.
94. Rose RG, Kelsey MP, Russel WO, Ibanez ML, White EC, LeeClark R. Follow-up study of thyroid cancer treated by unilateral lobectomy. *Am J Surg* 106:494, 1963.
95. Greenspan FS. Radiation exposure and thyroid cancer. *JAMA* 237:2089, 1977.
96. Crile G. Changing end results in patients with papillary carcinoma of the thyroid. *Surg Gynecol Obstet* 132:460, 1971.
97. Purves HD, Griesbach NE, Kennedy TH. Studies in experimental goiter; malignant change in a transplantable rat thyroid tumour. *Br J Cancer* 5: 301, 1951.
98. Leeper RD. The effects of ^{131}I therapy on survival of patients with metastatic papillary or follicular thyroid carcinoma. *J Clin Endocrinol Metab* 36:1143, 1973.

99. Bonte FJ, McConnel RW. Pulmonary metastases from differentiated thyroid carcinoma demonstrated only by nuclear imaging. *Radiology* 107:585, 1973.
100. Casara D, Zorat PL, Busnardo B, Girelli ME. Pulmonary metastases from differentiated thyroid carcinoma detected only by radionuclide imaging. *Br J Radiol* 54:362, 1981.
101. Attie JN, Moskowitz GW, Margouleff D, Levy LM. Feasibility of total thyroidectomy in the treatment of thyroid carcinoma. Postoperative radioactive iodine evaluation of 140 cases. *Am J Surg* 138:555, 1979.
102. Katz AD, Bronson D. Total thyroidectomy. The indications and results of 630 cases. *Am J Surg* 136:450, 1978.
103. Salander HE, Tisell LE. Incidence of hypoparathyroidism after radical surgery for thyroid carcinoma and autotransplantation of parathyroid glands. *Am J Surg* 134:358, 1977.
104. Thompson N, Harness JK. Complications of total thyroidectomy for carcinoma. *Surg Gynecol Obstet* 131:861, 1970.
105. Jereb B, Stjernswärd J, Löwhagen T. Anaplastic giant-cell carcinoma of the thyroid. A study of treatment and prognosis. *Cancer* 35:1293, 1975.
106. Brincker H, Hansen HS, Andersen AP. Induction of leucaemia by ¹³¹I treatment of thyroid carcinoma. *Br J Cancer* 28:232, 1972.
107. Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Ramagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. *Ann Surg* 184:541, 1976.
108. Verby JE, Woolner LB, Nobrega FT, Kurland LT, McConahey WM. Thyroid cancer in Olmstedt county 1935-1965. *J Natl Cancer Inst* 43:813, 1969.
109. Fletcher JR. Medullary (solid) carcinoma of the thyroid gland. A review of 249 cases. *Arch Surg* 100:257, 1970.
110. Russel CF, Van Herden JA, Sizemore GW, Edis AJ, Taylor WF, Remine WH, Carney JA. The surgical management of medullary thyroid carcinoma. *Ann Surg* 197: 42, 1983.
111. Lindahl F. Papillary thyroid carcinoma in Denmark, 1943-1968. *Cancer* 36:540, 1975.
112. Rafila S. Anaplastic tumors of the thyroid. *Cancer* 23:668, 1969.
113. Harwood J, Clark OH, Englebert Dunphy J. Significance of lymph node metastases in differentiated thyroid cancer. *Am J Surg* 136:107, 1978.

**The prevalence of thyroid disorders in a
middle-aged female population, with
special reference to the solitary
thyroid nodule**

S Borup Christensen, U B Ericsson, L Janzon,

S Tibblin, and E Trelle

Abstract

A survey of thyroid disease was conducted in 477 middle-aged women selected at random in an urban area where goiter is not endemic. The overall occurrence of thyroid disease was estimated to be 16.2%. Previously known disease was reported by 6.7% of those surveyed, and an additional 9.5% were diagnosed in the present study. The prevalence of all goiter was 11.3%, and of a palpable solitary nodule, 6.5%. Women with goiter were examined by thyroid scintigraphy and fine-needle aspiration cytology. The results of these examinations were considered a sufficient basis for benign diagnosis in all cases except one, a woman with a solitary nodule who was surgically treated because the cytologic report indicated follicular neoplasm; histopathology, however, revealed colloid goiter. The accumulated incidence of hyperthyroidism was 2.3% and of hypothyroidism 0.8%. It is concluded that goiter is a common disorder among women living in non-endemic areas, and that most goiter, including palpable solitary nodules, can be classified after evaluation as multinodular goiter.

Introduction

A lump in the neck is often the first and only physical sign of thyroid cancer. Many patients with thyroid nodules are referred for surgery because malignancy cannot be ruled out. To assess such nodules adequately, it is important to know the prevalence of thyroid lesions in an unselected population. This is particularly true for solitary nodules, in which the risk of malignancy is considered to be the highest (Gogas, Katsikas, Sechas, Kakaviatos & Skalkeas, 1976; Hoffman, Thompson & Heffron, 1972; Messaris, Kyriakou, Vasilopoulos & Tountas, 1974). Most previous studies of goiter prevalence dealt with all goiter; generally no classification in subgroups has been done (Kelly & Snedden, 1960).

The present survey was undertaken to evaluate the prevalence of goiter in a well-defined female population, with particular reference to palpable solitary nodules. An analysis of the findings by palpation and a more thorough description of thyroid morbidity are presented.

Material

The investigation was performed at the Department of Preventive Medicine in Malmö, Sweden. Malmö, situated in the southern part of the country, has a population of 235,000, which is stable, with only minor movements in the particular population studied. Malmö is mainly urban. Goiter is considered non-endemic to the area (Höjer, 1931).

During a seven-month period in 1979, 863 women, born in the years 1926 and 1931, were selected at random from the city council registry and invited for a health screening program concerning carbohydrate metabolism and hypertension. The invited group corresponded to one third of the total female population born during those years. The invitation was accepted by 597 women (69.2%). Of these women 477 were invited to participate in the present thyroid study and all agreed; 120 women were not invited to the

thyroid study, because, for practical reasons, this opportunity could not be offered every day during the time the screening study was running. No women were excluded intentionally. From the group of 266 individuals who did not accept the invitation for health screening, 95 women were selected at random to answer a questionnaire concerning thyroid disease.

Methods

All women had a clinical examination, including evaluation of thyroid function and inspection and palpation of the neck by one physician (investigator I). This investigator and investigator II were trained clinicians with particular interest in thyroid disease. At the physical examination, the presence or absence of goiter was noted. Goiter was defined as an enlargement of the thyroid and/or a deviation of its form and consistency making parts of the gland or the whole gland visible or palpable. Positive physical findings were classified as diffuse enlargement, multiple nodules, or a solitary nodule. The largest diameter of a solitary nodule was recorded in centimeters.

After the clinical examination, all participants answered a questionnaire that included family history of thyroid disease, previous thyroid morbidity, signs of disturbance of thyroid function, current medication, and certain environmental factors. In individuals with previous thyroid disease the medical records were studied.

Before the clinical examination, a fasting blood sample was taken for the following tests: S-triiodothyronine (T_3), S-thyrotropin (TSH), S-thyroglobulin (Tg) and thyroglobulin antibodies (TA). Radioimmunoassays were used to determine T_3 , TSH, and Tg (Thorell & Larsson, 1978; Van Herle, Uller, Matthews & Brown, 1973a). The reference values are as follows: T_3 , 0.9 to 3.2 nmol/l; TSH, <8 mU/l; Tg, <40 μ g/l. TA was analyzed with a passive hemagglutination test using a commercial kit (Wellcome Research Laboratories, Bechenham, England). Titers of one tenth or more were considered positive.

T_3 levels were classified as high (≥ 2 nmol/l) or low (< 2 nmol/l). TSH levels also were classified as high (≥ 4 mU/l) or low (< 4 mU/l). These subgroups were correlated with the anamnestic and clinical findings.

All individuals who were found to have a goiter and the individuals in whom T_3 or TSH were above the normal range were offered a special examination comprising thyroid scintigraphy (using sodium pertechnetate Tc 99m) and aspiration biopsy cytology. In addition, the blood tests were repeated. Individuals who accepted the offer also underwent a clinical examination and evaluation by investigator II. This physician was aware that deviating clinical or laboratory data had been found, but he did not know the particular deviation. Investigator II decided on further treatment.

Weight and height were measured in all participants. To evaluate the deviations from normal weight, an index was used with the formula

$$\frac{\text{weight (kg)} + 100}{\text{height (cm)}}$$

For statistical analysis, the chi square test and the binominal formula were used.

Results

NON-PARTICIPANTS

After up to two reminders, 61 of 95 women answered the questionnaire (64.2%). Seven of these (11.5%) reported previous thyroid disease; three had been operated on for goiter and four underwent medical treatment of thyroid disease. The prevalence of anamnestic thyroid disease in the participant group was 5.6%. The difference between the participant and non-participant groups of 5.9% is not statistically significant ($0.05 < p < 0.07$).

PARTICIPANTS

First clinical examination

On physical examination, a palpable goiter was found in 54 women (11.3%). Twenty of these goiters were visible, and four women with visible goiter were aware of it. Previously unrecognized palpable goiter was present in 45 women (9.5%). Palpable solitary nodules were present in 31 women (6.5%). One of these was more than 3 cm in diameter; 21 had diameters of less than 2 cm. Multiple nodules were present in 17 participants and diffuse enlargement in six.

Thyroid laboratory tests

T_3 was normally distributed (mean $1.65 \text{ nmol/l} \pm 0.34 \text{ SD}$). Three patients had values below the normal range, but none of these had elevated TSH. In three women T_3 values above 3.2 nmol/l were found.

The distribution of TSH was positively skewed: Median value was 2.7 mU/l , the 95th percentile was less than 5 mU/l , and the 90th percentile was less than 4 mU/l . In six women TSH values above the normal range were noted (8 to 24 mU/l). All of these had T_3 values within the normal range.

Also, the distribution of T_g was positively skewed with the median $19.5 \text{ } \mu\text{g/l}$ and the 95th percentile $< 56 \text{ } \mu\text{g/l}$. Sixty-seven women (14.0%) had $T_g \geq 40 \text{ } \mu\text{g/l}$. Titers of TA $\geq 1/10$ were present in 23 women (4.8%, range $1/10$ to $1/1280$).

Second clinical examination

Sixty-two women were invited to the second clinical examination. Of these, 53 had goiter and normal levels of T_3 and TSH. One had goiter and elevated T_3 . Eight women had functional disturbances without goiter, six of them with elevated TSH and two with elevated T_3 . Seven women (four with a solitary nodule, three with diffuse enlargement), did not attend the second investigation. Table I presents the palpation findings in the

47 women investigated by both physicians. Two of the palpation findings by investigator I could not be confirmed by investigator II.

Table I: Results of physical examination of 47 patients by two physicians.

Findings	Investigator I	Investigator II
Solitary nodule	27	24
Multiple nodules	17	17
Diffuse enlargement	3	4
Normal	-	2

Comparison of results

In table II the palpation findings from the first investigation are compared to results of scintigraphy.

Table II: Thyroid scanning results compared with palpation findings from first examination of 47 patients.

Scanning	PRIMARY PHYSICAL FINDINGS		
	Solitary (n = 27)	Multiple (n = 17)	Diffuse (n = 3)
Normal or diffuse (n=20)	13	5	2
Cold, solitary (n=2)	2	-	-
Hot, solitary (n=4)	3	1	-
Multiple (n=21)	9	11	1

Of the 27 nodules that were considered solitary by palpation, 13 could not be recorded in the scintigram. In five of the solitary nodules there was concordance between palpation and scintigram. Nine nodules that were thought to be solitary by palpation were found to be multinodular on the scintigram. At the physical examination multiple nodules were found in 17 women. Of these, 11 also showed multinodularity on the scintigram.

Table III compares the palpation findings of the first examination to cytology. Of the 27 women with a solitary nodule by palpation 18 had an aspiration cytology indicating goiter rather than neoplasia as judged from abundant yield of colloid with scanty follicular epithelium, sometimes showing admixture of Askanazy cells and macrophages. In one case the cytology specimen was dominated by Askanazy cells, indicating follicular tumor. In no case was there cytologic suspicion of malignancy.

Table III: Cytology results compared with palpation findings from first examination in 47 patients.

Cytology	PRIMARY PHYSICAL FINDINGS		
	Solitary (n = 27)	Multiple (n = 17)	Diffuse (n = 3)
Colloid goiter (n=34)	18	15	1
Follicular tumor (n=1)	1	0	0
Thyroiditis (n=5)	2	2	1
Miscellaneous (n=3)	3	0	0
Not evaluable (n=4)	3	0	1

One of the three women with elevated T_3 at the first examination had a multinodular goiter and elevated T_3 at the second investigation. The remaining two had T_3 within normal range at the control examination and were considered free from thyroid disease.

Elevated TSH, which was found in six women at the first examination, remained the same at control. Three of these women were previously treated for thyrotoxicosis. Two had a nodular goiter, one of which showed cytological signs of thyroiditis. None of these goiters were found at the first examination. One woman had an elevated TSH without any other signs of thyroid disease. None of the women with elevated TSH had clinical or laboratory signs of overt hypothyroidism, nor were any TA titers positive. All women with a palpable goiter at the first examination had TSH-values within the normal range.

The first palpation findings and the final diagnoses following the second examination are contrasted in table IV. For 36 women, the final diagnosis was multinodular goiter. Of these, 22 were considered at the first investigation to have a solitary nodule; 14 were thought, at first, to have multinodular goiter. None of the three women with "hot adenoma" had clinical signs of thyrotoxicosis or elevated T_3 . Of the five women with cytologically verified thyroiditis, two had a slight elevation of TA. One patient with a solitary cold nodule on the scintigram and Askanazy cells in the fine-needle aspirate underwent hemithyroidectomy, but histopathological examination revealed colloid goiter. The other woman with a solitary cold nodule on the scintigram refused further treatment. The woman with thyrotoxicosis was treated surgically later. The other women have not been treated, neither medically nor surgically, but were subjected to follow-up. During the following three years of observation, three additional patients were treated. One woman, who had a 1 cm thyroid nodule considered to be part of a multinodular goiter, underwent hemithyroidectomy 2.5 years after the initial investigation due to growth of the nodule; histopathological examination showed colloid goiter. Thyroxine treatment was instituted in two women with a diagnosis of thyroiditis because TSH levels increased.

Table IV: Final diagnosis compared to primary physical findings in 54 patients.

FINAL DIAGNOSIS	PRIMARY PHYSICAL FINDINGS			Total
	Solitary nodule (n = 31)	Multiple nodules (n = 17)	Diffuse enlargement (n = 6)	
Nodular goiter	22	14	-	36
Thyroiditis*	2	2	1	5
Diffuse goiter	-	-	5	5
"Hot adenoma"	3	-	-	3
Solitary nodule **	4	-	-	4
Thyrotoxicosis (Plummer's disease)	-	1	-	1

* Positive cytology

** Incomplete investigation

History of thyroid disease

Previously known thyroid disease was reported by 32 women (6.7%, figure 1). Thirteen women (2.7%) had been surgically treated for goiter. None was treated for thyroid cancer. Nine women had euthyroid goiter; five of these were being treated with thyroxine. Five women had been treated medically for thyrotoxicosis, two with antithyroid drugs and three with ^{131}I . Two women had a previous history of chronic thyroiditis but neither showed elevated TA. Current medication with thyroxine in various doses occurred in 20 women (4.2%).

Prevalence of disturbances in thyroid function

The accumulated incidence of hyperthyroidism was 2.3% (one case was identified in the present survey, ten cases had been diagnosed earlier). Hypothyroidism was present in six women with all cases previously known.

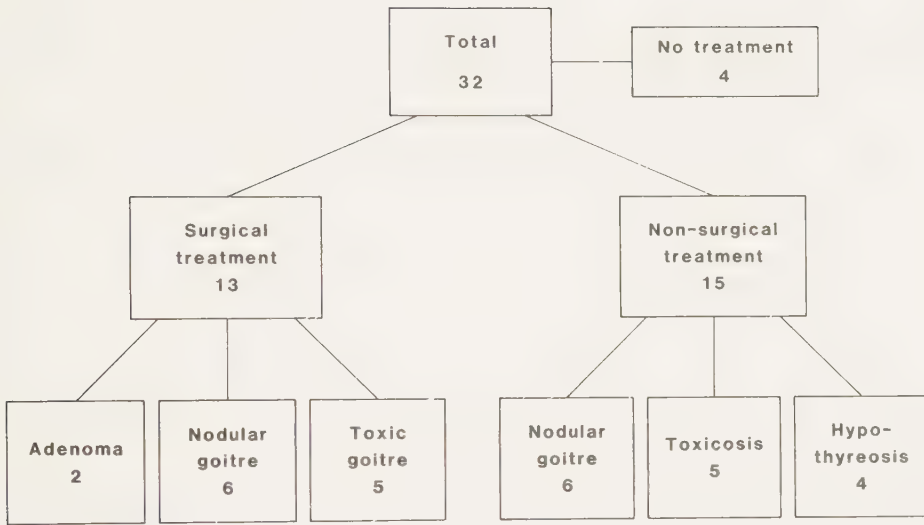


Fig 1: History of participants with previously known thyroid disease.

Two of these cases were late complications of treatment for thyrotoxicosis, thus primary hypothyroidism was present in four women (0.8%).

Thyroid morbidity related to thyroid tests and weight

In table V, goiter and previously known thyroid disease have been correlated to thyroid tests and weight index. In the goiter group, six women had received thyroxine treatment. T_3 and TSH were not correlated to palpable goiter, even if individuals taking thyroxine were excluded from the goiter group. There was correlation between goiter and positive TA ($p < 0.001$) and between anamnestic thyroid disease and elevated TSH ($p < 0.05$). Two of eight women with positive TA and goiter had a cytology finding indicating thyroiditis. Elevated Tg level was more frequent in the goiter group

Table V: Thyroid abnormalities correlated to T_3 , TSH, TA, Tg, and weight index in 477 women screened for thyroid disease.

		Palpable goiter* (n=54)	History of thyroid disease without goiter** (n=23)	No thyroid disease (control group)(n=400)
T_3	≥ 2 nmol/l	(n=65)	4 (17%)	52 (13%)
	< 2 nmol/l	(n=413)	19	348
TSH	≥ 4 mU/l	(n=48)	5 (22%)($p<0.05$)	35 (9%)
	< 4 mU/l	(n=430)	18	365
TA	$\geq 1/10$	(n=23)	1 (4%)	14 (3%)
	$< 1/10$	(n=455)	22	386
Tg	≥ 40 μ g/l	(n=67)	2 (9%)	49 (12%)
	< 40 μ g/l	(n=411)	21	351
weight index	≥ 1.10	(n=134)	6 (26%)	113 (28%)
	< 1.10	(n=344)	17	287

* Six treated with thyroxine

** Includes previous

thyroid operations (13),
thyrotoxicosis, treated medically (4),
hypothyroidism (4), and treatment with
thyroxine for unknown indications (2).

than among the controls ($p < 0.001$). Dividing the elevated Tg levels in two subgroups, one with slightly elevated Tg (Tg between 40 and 59 $\mu\text{g/l}$) and another with markedly elevated Tg (Tg $\geq 60 \mu\text{g/l}$), a statistical correlation to goiter was found in the latter group ($p < 0.001$).

There was no significant correlation between T_3 and TSH levels and such symptoms of disturbed thyroid function as heat intolerance, tachycardia, tremor, or fatigue. Each of these symptoms occurred more frequently in postmenopausal women ($p < 0.01$).

Discussion

Morbidity among participants in population surveys is often an underestimation of the morbidity in the population (Wilhelmsen, Ljungberg, Wedel & Werkö, 1976; Tibblin, 1965). Part of the explanation for this may be that individuals already under treatment for known disease abstain from further investigations. In the present study the occurrence of known thyroid disease among non-participants was 5.9% higher than among participants. The difference is not significant, but it can be assumed that the prevalence of thyroid disease found in the participant group is not an overestimation of the prevalence in the corresponding population.

Several attempts have been made to classify goiters according to size (Perez, Scrimshaw & Munoz, 1960; Stanbury, Ermans, Hetzel, Pretell & Querido, 1974; Kilpatrick, Milne, Rushbrooke, Wilson ESB & Wilson GM, 1963). In the present investigation the main purpose was to establish the prevalence of thyroid nodules, which should be easier to delimit than the extent of thyroid enlargement. Lack of concordance between the investigators concerning the findings by palpation occurred in three cases (table I). In all of these, a nodule solitary by palpation, was diagnosed at the first examination; at the second examination the thyroid was considered normal by palpation in two of these cases, while a diffuse enlargement was found in one case. Certain differences could be expected because

most of the findings were discrete. In fact, the variation between observers in the present study was modest compared with that found by other authors (Dingle, Ferguson, Horn, Tubmen & Hall, 1966). It is reasonable to assume that the observed prevalence of goiter (11.3%) is not an overestimation of the occurrence in the participant group, and that the number of palpable solitary nodules corresponds at least to the number found by both investigators, that is, 24 (5.0%).

The observed prevalence of goiter corresponds well to figures from other recently published surveys in non-endemic areas. In England, Tunbridge, Evered, Hall, Appleton, Brewis, Clark, Grimley Evans, Young, Bird & Smith (1977) found a prevalence among females of about 15%; Dingle et al, about 12%. The primary aim of the present investigation was to evaluate the prevalence of solitary nodules. The figure of 6.5% reported here agrees well with the figures from a study in Framingham, Massachusetts (Vander, Gaston & Dawber, 1954) where solitary nodules were recorded in 4.6% of the female population. In that study 28 of 133 patients with solitary nodules were operated but no malignancy was revealed. In the present study also no signs of thyroid cancer were found. This is in striking contrast to results published in the surgical literature which report frequencies of cancer in solitary nodules to be 8 to 30 per cent (Gogas et al; Hoffman et al; Brooks, 1973).

The final diagnosis in table IV was based upon clinical examination, thyroid scan and fine-needle aspiration cytology. The cytology findings are considered most important as far as malignancy is concerned. In no case did the cytology finding indicate thyroid cancer. However, the specificity of this procedure is considered rather low (Einhorn & Franzen, 1962; Walfish, Hazani, Strawbridge, Miskin & Rosen, 1977), mainly because it is impossible for the cytologist to differentiate between follicular cancer and adenoma. If all cytologically follicular tumors are regarded as cancer suspicious, the specificity will increase (Ann Int Med, 1977). In one patient the cytology finding indicated follicular tumor. In this case Askanazy cells were found in the cytology aspirate, but histopathological examination after hemithyroidectomy revealed multinodular goiter.

Follicular tumors were not suspected in any of the other specimens; therefore the authors consider a cancer diagnosis unlikely in the patients examined cytologically.

Only 7.4% of the solitary nodules found on palpation were solitary and non-functioning (cold) on the thyroid scan. This is in discrepancy with figures from clinical materials where "solitary, cold nodules" occur more frequently (Messaris et al; Sykes, 1981), probably because of patient selection. Of 27 nodules, considered to be solitary on palpation, nine (33%) were found to be multinodular on scintigram, and three (11%) were hot. Since malignancy in hot and multiple nodules is unlikely, the scintiscan considerably reduced suspicion of malignancy in 44% of subjects.

The prevalence of cancer in solitary nodules cannot be estimated from the present survey because the number of participants is too small. From an extensive population survey in Nagano, Japan, Maruchi, Furihata & Makiuchi (1971) estimated the cancer prevalence in women to be 185 in 100,000 approximately 80 times the annual incidence registered. Probably, the thyroid cancer prevalence in Malmö also is considerably higher than the annual incidence, which in 1977 was 7.5 in 100,000 women (The Cancer Registry, 1981). If it is assumed that thyroid cancer prevalence in Malmö is the same as in Nagano, then palpable thyroid cancer should comprise about 3% of solitary nodules in women.

The finding of solitary nodules in an unselected middle-aged female population is common. Although the probability of cancer is low, further examination is indicated. Should this include fine-needle aspiration biopsy, thyroid scan, or both? This important question cannot be evaluated satisfactorily on the basis of the results from the present study, because these do not allow calculation of sensitivity and specificity of the procedures. From other studies, however, it is apparent that the specificity of the cytologic examination is superior to that of thyroid scan, whereas the sensitivity is almost equal (Van Herle, Rich, Ljung, Ashcraft, Solomon & Keeler, 1982b). The cost of the cytology procedure is calculated to be only half of the cost for technetium scan in Malmö. Therefore it

seems reasonable to use cytology as the primary screening procedure and, in selected cases, supplement the investigation by thyroid scan.

The 2.3% accumulated incidence of hyperthyroidism is considered well-founded. In the Whickham survey (Tunbridge et al) a similar estimate was made; their figure for "established hyperthyroidism" was 2% (women, all ages). The criteria for diagnosis of hypothyroidism are more uncertain, so estimation of prevalence becomes more uncertain. Four women had a known idiopathic hypothyroidism when they attended the survey; no new cases were found. In the Whickham survey the prevalence of "established hypothyroidism" was 1.1% among women. The six women in the present study with elevated TSH without signs of overt hypothyroidism are subjects of further follow-up, since other studies have indicated that such individuals are at increased risk for later development of hypofunction (Nyström, Bengtsson, Lindquist, Noppa, Lindstedt & Lundberg, 1981).

Several epidemiological studies concerning the occurrence of thyroid antibodies have been published (Dingle et al; Tunbridge et al; Gordin, Saarinen, Heinonen & Lamberg, 1972). Comparison of figures from such studies is difficult partly due to the use of different methods for analysis and partly due to variance in normal range. In contrast to Dingle et al, the present authors found a significant correlation between goiter and TA. The present study, however, could not confirm the correlation between TSH and TA reported by other authors (Tunbridge et al; Gordin et al). Correlation between thyroiditis, as verified by cytology, and elevated TA was poor, and it is concluded that TA is of limited value in establishing the diagnosis of thyroiditis.

Thyroglobulin was elevated in 30% of the women with goiter and in 12% of the women without known thyroid disease. This confirms earlier studies of a correlation between goiter and elevated Tg levels (Levine, Hershman, Van Herle & Deftos, 1978; Pezzino, Vigneri, Squatrito, Filetti, Camus & Polosa, 1978). The women with elevated Tg and no known thyroid disease are subjects for further studies and follow-up.

The solitary thyroid lump is often the only sign of a thyroid cancer. Excision of such lumps is advocated in one of the leading surgical textbooks (Schwartz, Shires, Spencer & Storer, 1979). From the present survey, the authors conclude that finding of a solitary nodule by palpation is common, at least in middle-aged women. Clinical examination supplemented by scintigraphy and cytology should provide a reasonable basis for exclusion of malignancy. The present authors consider an uncritical surgical excision of all palpable solitary thyroid lumps unnecessary and undesirable.

Acknowledgements

We would like to express our gratitude to Professor Arne Forsgren and his staff at the Department of Bacteriology, Malmö General Hospital, for the thyroglobulin antibody analyses.

References

- Ann Int Med, Editorial: Managing the solitary thyroid nodule: Role of needle biopsy, 1977. *Ann Int Med* 87, 375.
- Brooks, J.R. 1973. The solitary thyroid nodule. *Am J Surg* 125, 477.
- Cancer incidence in Sweden 1977. National Board of Health and Welfare. Stockholm: The Cancer Registry, 1981, 66.
- Dingle, P.R., Ferguson, A., Horn, D.B., Tubmen, J. & Hall, R. 1966. The incidence of thyroglobulin antibodies and thyroid enlargement in a general practice in north-east England. *Clin Exp Immunol* 1, 277.
- Einhorn, J. & Franzen, S. 1962. Thin-needle biopsy in the diagnosis of thyroid disease. *Acta Radiol (Stockholm)* 58, 321.
- Gogas, J.G., Katsikas, D., Sechas, M., Kakaviatos, N. & Skalkeas, G.D. 1976. Prediction of malignancy in solitary thyroid nodeules in a country with endemic goiter. *Am J Surg* 132, 623.
- Gordin, A., Saarinen, P., Heinonen, O.P. & Lamberg, B.-A. 1972. Serum-thyrotrophin in symptomless autoimmune thyroiditis. *Lancet* 1, 551.
- Hoffman, G. L., Thompson, N.W. & Heffron, C. 1972. The solitary thyroid nodule: A reassessment. *Arch Surg* 105, 379.
- Höjer, J.A. 1931. Kropfstudien. *Svenska Läkaresällskapets handlingar* 57 (1), 1.
- Kelly, F.C., Snedden, W.W. 1960. Prevalence and geographic distribution of endemic goitre. In: *Endemic goitre. WHO monograph 44*. Geneva: World Health Organization, pp 27.
- Kilpatrick, R., Milne, J.S., Rushbrooke, M., Wilson, E.S.B. & Wilson, G.M. 1963. A survey of thyroid enlargement in two general practices in Great Britain. *Br Med J* 1, 29.
- Levine, G.A., Hershman, J.M., Van Herle, A.J. & Deftos, L.J. 1978. Thyroglobulin and calcitonin in patients with non-toxic goiter. *JAMA* 240, 2282.
- Maruchi, N., Furihata, R. & Makiuchi, M. 1971. Population surveys on the prevalence of thyroid cancer in a non-endemic region, Nagano, Japan. *Int J Cancer* 7, 575.
- Messararis, G., Kyriakou, K., Vasilopoulos, P. & Tountas, C. 1974. The single thyroid nodule and carcinoma. *Br J Surg* 61, 943.

- Nyström, E., Bengtsson, C., Lindquist, O., Noppa, H., Lindstedt, G. & Lundberg, P.A. 1981. Thyroid disease and high concentration of serum thyrotrophin in a population sample of women: A 4-year follow-up. *Acta Med Scand* 210, 39.
- Perez, C., Scrimshaw, N.S., Munoz, J.A. 1960. Technique of endemic goitre surveys. In: *Endemic goitre*. WHO monograph 44. Geneva: World Health Organization, pp 369.
- Pezzino, V., Vigneri, R., Squatrito, S., Filetti, S., Camus, M. & Polosa, P. 1978. Increased serum thyroglobulin levels in patients with nontoxic goiter. *J Clin Endocrinol Metab* 46, 653.
- Schwartz, S.I., Shires, G.T., Spencer, F.C. & Storer, E.H. (eds). 1979. *Principles of Surgery*, 3rd ed. New York: McGraw-Hill, pp 1564.
- Stanbury, J.B., Ermans, A.M., Hetzel, B.S., Pretell, E.A. & Querido, A. 1974. Endemic goiter and cretinism: Public health significance and prevention. *WHO Chron* 28, 220.
- Sykes, D. 1981. The solitary thyroid nodule. *Br J Surg* 68, 510.
- Thorell, J.I. & Larson, S.M. 1978. *Radioimmunoassay and related techniques: Methodology and clinical applications*. St Louis: CV Mosby.
- Tibblin, G. 1965. A population study of 50-year-old men. An analysis of the non-participation group. *Acta Med Scand* 178, 453.
- Tunbridge, W.M.G., Evered, D.C., Hall, R., Appleton, D., Brewis, M., Clark, F., Grimley Evans, J., Young, E., Bird, T. & Smith, T.A. 1977. The spectrum of thyroid disease in a community: The Wickham survey. *Clin Endocrin* 7, 481.
- Walfish, P.G., Hazani, E., Strawbridge, H.T.G., Miskin, M. & Rosen, I.B. 1977. Combined ultrasound and needle aspiration cytology in the assessment and management of hypofunctioning thyroid nodule. *Ann Int Med* 87, 270.
- Vander, J.B., Gaston, E.A. & Dawber, T.R. 1954. Significance of solitary nontoxic thyroid nodules: Preliminary report. *N Engl J Med* 251, 970.
- Van Herle, A.J., Uller, R.P., Matthews, N.L. & Brown, J. 1973. Radioimmunoassay for measurement of thyroglobulin in human serum. *J Clin Invest* 52, 1320.

- Van Herle, A.J., Rich, P., Ljung, B.M.E., Ashcraft, M.W., Solomon, D.H. & Keeler, E.B. 1982. The thyroid nodule. *Ann Intern Med* 96, 221.
- Wilhelmsen, L., Ljungberg, S., Wedel, H. & Werkö, L. 1976. A comparison between participants and non-participants in a primary preventive trial. *J Chron Dis* 29, 331.

**Prediction of malignancy in the solitary
thyroid nodule by physical examination,
thyroid scan, fine-needle aspiration
biopsy cytology, and serum thyroglobulin**

A prospective study of 100 patients,
surgically treated

S Borup Christensen, L Bondesson,

U B Ericsson and K Lindholm

Abstract

One hundred consecutive patients with a thyroid nodule, solitary by palpation, selected for surgery, were studied prospectively. Anamnestic data, findings at physical examination, thyroid scan, and fine-needle aspiration biopsy (ABC) and serum thyroglobulin (Tg) values were correlated with the histopathologic diagnoses (HD) following surgery. Eighteen patients had an HD of malignant tumor while 82 had a benign diagnosis. Familial occurrence of benign goiter was reported more frequently by patients with a benign HD (46%) than by those with a malignant HD (11%). Nodules found to be hard by palpation (n=11) were more frequently malignant (n=7) than benign (n=4). Nodules appearing as "hot" on scintigram (n=12) were all benign, whereas 22% of 59 "solitary cold nodules" were malignant. The cytologic specimens were reviewed and reclassified. The sample obtained by ABC was insufficient for cytologic diagnosis (CD) in eleven cases. Four patients had a correct CD of papillary cancer. Of 36 patients with the CD "neoplasia" (malignant or benign) 33% had an HD of malignant tumor, 56% of follicular adenoma, and 11% of colloid goiter. Forty-seven patients had a benign CD; one of them was false negative but the index nodule did not, in this case, correspond to the underlying cancer. The Tg level was significantly higher in patients with thyroid cancer than in those with benign disorders but the predictive value of the test was low. Tg values of more than ten times the upper normal range only occurred in patients with either thyroid cancer (n=3) or thyrotoxicosis (n=2).

The factors and methods mentioned above were all considered of value in the management of patients with a solitary thyroid nodule, ABC being the best single method. Patients with a CD of malignancy or neoplasia should be considered for surgery, whereas for most patients with a benign CD careful follow-up will suffice.

Introduction

The prevalence of thyroid nodules, solitary by palpation, in the unselected population is high with reported rates of three to six per cent (1,2), whereas the prevalence of palpable thyroid carcinoma is probably in the region of 0.05 to 0.15 per cent (3). Since a solitary nodule is the most common sign of thyroid carcinoma (4) there is a need of inexpensive, simple and safe methods to identify correctly those nodules which have to be excised because of malignancy. Besides clinical examination, the most frequently used methods have been different forms of radioactive imaging and fine-needle aspiration biopsy cytology (ABC). Particularly ABC has been shown to be useful in the evaluation of malignancy in thyroid nodules (5-10). Still, however, many benign nodules have to be excised for biopsy in order to find the malignant tumors. Therefore, further attempts to refine the existing methods, and to introduce new ones, are desirable.

The present study was undertaken to gain further information on the usefulness of anamnestic data, physical examination, thyroid scan, and ABC in the prediction or ruling out of malignancy in palpable solitary thyroid nodules. Moreover, the benefit of serum thyroglobulin (Tg) in differentiating between malignant and benign nodules was evaluated.

Material and Methods

One hundred consecutive patients with a thyroid nodule, solitary by palpation, selected for surgical treatment at our department during a three-year period, were collected prospectively. The selection for surgery was made before the patients were included in the present study. In 82 patients the main indication for surgery was suspicion of malignancy, in twelve patients thyrotoxicosis (solitary "hot adenoma"), and in six patients cosmetic complaints or pressure symptoms. The suspicion of malignancy was in 75 patients based on a cytology report indicating neoplasm and/or a thyroid scan showing a "solitary, cold spot", in seven patients on other clinical symptoms or signs. Serum thyroglobulin (Tg) was not used as a diagnostic

tool. The twelve patients with thyrotoxicosis had received antithyroid drugs and thyroxine and were all euthyroid at the time of surgery. Current medication with thyroxine occurred in 18 of the 88 patients with atoxic goiter.

Before the surgical procedure, each patient was interviewed and examined according to a standard form which included information on anamnestic data and the results of the clinical examination. In 91 cases the interview and the physical examination were made by one of the authors (SBC) and in nine cases by another physician. The day before surgery a venous blood sample was drawn for determination of Tg and thyroglobulin antibodies (TgA). Thyroid scan (using ^{99}Tc -pertechnetate) had been performed in 96 patients before admission to hospital, ABC in 98 patients.

The puncture for cytologic examination was always performed by a cytologist who generally had access to the thyroid scan. The technique and preparation of smears were essentially the same as described by Löwhagen et al 1979 (6). All slides were reviewed and reclassified independently by two cytologists who had no knowledge of the final histopathologic diagnosis or of the results of other diagnostic procedures. Whenever there was lack of accordance on the cytologic diagnosis, both cytologists together reviewed the particular slides and agreed on a diagnosis. The results of the ABC were then grouped according to the following classification: malignant, neoplasia (including suspected neoplasia), benign (colloid goiter and/or thyroiditis) and not evaluable (insufficient material). The basic principles for this classification conform with criteria advocated by others (11,12).

The result of thyroid scan was classified according to the original reports. Tg was determined by radioimmunoassay (13); the minimum detectable level was 2 $\mu\text{g/l}$, the reference value for normality used in this hospital was below 40 $\mu\text{g/l}$. TgA was analyzed with a passive hemagglutination test using a commercial kit (Wellcome Research Laboratories, Beckenham, England). Subjects with a TgA titer of 1:10 or more ($n=7$) were excluded from analysis relating to Tg.

The histopathologic material following surgery was revised by one patholo-

gist. The histopathologic finding corresponding to the clinically observed (and cytologically examined) nodule was, except in one case (see below) considered main diagnosis, whereas histopathologic findings in other parts of the gland were considered additional diagnoses. Eighteen patients had a main diagnosis of malignant thyroid tumor, 41 of follicular adenoma, 40 of colloid goiter and one of thyroiditis. According to the WHO classification (14), ten of the 18 malignant tumors were papillary carcinomas, seven follicular carcinomas, and one a malignant lymphoma. Three patients with a benign main diagnosis had an additional diagnosis of occult papillary carcinoma. These were all less than 5 mm in their largest diameter.

STATISTICS

The Man Whitney rank sum test for unpaired observations was used in calculations relating to Tg. The chi-square test was used in the other statistical calculations.

Results

The age and sex distribution and the main diagnoses following surgery are contrasted in figure 1. Of the men, 29% had a diagnosis of malignant tumor, whilst the corresponding figure in women was 16%. The rate of malignancy was 14% in patients below the age of 40, 13% in patients aged 40 to 59, and 44% in patients aged 60 or more.

ANAMNESTIC DATA AND PHYSICAL EXAMINATION (Table I)

The final diagnosis was more often benign than malignant in patients with a family history of benign goiter ($p < 0.01$). Nodules hard by palpation were more frequently malignant than benign ($p < 0.001$). The proportion of patients with a final diagnosis of malignancy was not significantly influenced by the duration of known goiter, by the growth of the nodule during the last

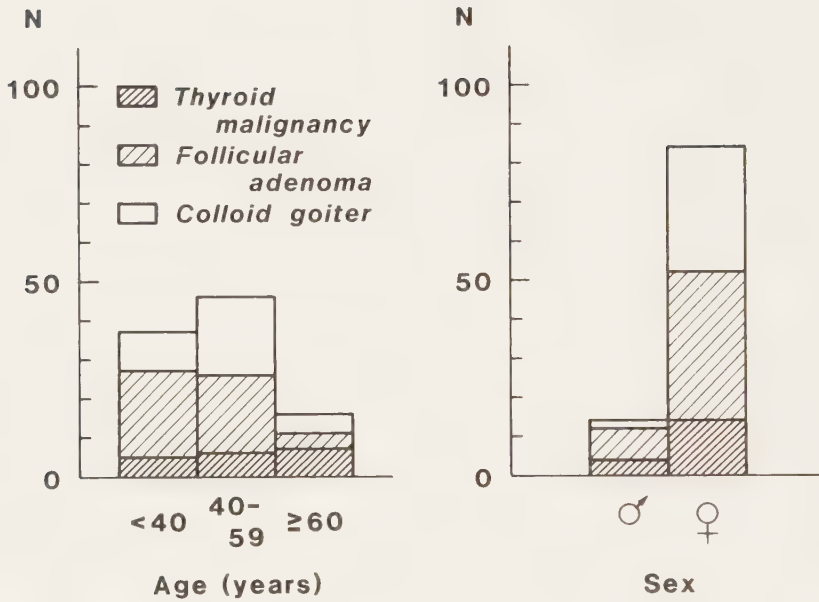


Fig 1: Age and sex distribution related to the histopathologic diagnosis in 100 patients surgically treated for a solitary thyroid nodule.

six months before surgery, or by the estimated size of the thyroid nodule.

THYROID SCAN (Table II)

Two of the patients with a thyroid scan indicating multiple nodules had a main diagnosis of papillary carcinoma and an additional diagnosis of colloid goiter. Of the 46 patients having a "solitary, cold spot" on scintigram and a benign main diagnosis, 22 had a follicular adenoma and 24 a colloid goiter.

Table I: Anamnestic data and results of physical examination related to the final histopathologic diagnosis in 100 patients with a solitary thyroid nodule.

Anamnestic data and palpatory findings	Histopathologic findings	
	Thyroid malignancy (n = 18)	Benign diagnosis (n = 82)
Familial disposition (benign goiter)	2 (11%) p<0.01	38 (46%)
History more than 6 months	7 (39%) ns	45 (55%)
Growth last 6 months	5 (28%) ns	31 (38%)
Nodule 3 cm or more in size	6 (33%) ns	14 (17%)
Nodule hard by palpation	7 (39%) p<0.001	4 (5%)
Nodule fixed by palpation	3 (17%) ns	1 ^{*)} (3%)

*) Previous thyroid surgery

Table II: The results of thyroid scan in 96 patients with a palpable solitary thyroid nodule related to the histopathologic diagnoses following surgery

Thyroid scan	Histopathology	
	Thyroid malignancy (n = 15)	Benign diagnosis (n = 81)
Cold solitary (n=59)	13 (22%)	46 (78%)
Hot solitary (n=12)	0	12
Multiple nodules (n=13)	2 (15%)	11 (85%)
Normal or "warm" (n=12)	0	12

ASPIRATION BIOPSY CYTOLOGY (Table III)

Four patients had a correct cytologic diagnosis of papillary carcinoma. The cytologic diagnosis was benign (colloid goiter) in one woman with a main diagnosis of papillary carcinoma. This patient had a large, deeply situated, recurrent cancer which was, however, covered by an overlying colloid goiter representing the clinically palpable nodule. The case of thyroiditis was correctly diagnosed by cytology. The remaining 46 patients with "benign cytology" all had a cytologic diagnosis of colloid goiter. Material insufficient for diagnosis was obtained from eleven patients, one of whom had a malignant tumor. This was an unusual follicular carcinoma with a large central calcification.

Table III: The results of fine-needle aspiration biopsy cytology in 98 patients with a palpable solitary thyroid nodule related to the histopathologic diagnoses following surgery

Cytologic diagnosis	Histopathologic diagnosis			
	Malignant (n = 18)	Follicular adenoma (n = 40)	Colloid goiter (n = 39)	Thyroiditis (n = 1)
Malignant (n=4)	4	-	-	-
Neoplasia NOS ¹⁾ (n=36)	12	20	4	-
Benign ²⁾ (n=47)	1	14	31	1
Sample insufficient for diagnosis (n=11)	1	6	4	-

1) NOS: not otherwise specified, i.e. malignancy neither proven nor ruled out. Includes 14 cases of "neoplasia suspected".

2) Colloid goiter (n=46) or thyroiditis (n=1).

SERUM THYROGLOBULIN (Figure 2)

The Tg values in the 18 patients with a malignant tumor were significantly higher than the values in the patients with a benign diagnosis ($p < 0.01$). The sensitivity of the test was 83% and the specificity 46% when Tg below 40 $\mu\text{g/l}$ was used as reference value. Three patients with a thyroid carcinoma and two patients with thyrotoxicosis had Tg values above 500 $\mu\text{g/l}$. There was no significant difference in the Tg level between patients with follicular adenoma and colloid goiter, respectively.

Discussion

In the evaluation of tumors in other sites than the thyroid gland, factors such as the duration of the history or growth rate, or signs such as size, consistency and form are often valuable in the differentiation between benign and malignant tumors. It is apparent from table I that these parameters are of limited value in the evaluation of the solitary thyroid nodule. Nodules hard by palpation were more frequently malignant than benign; this sign should thus be regarded as an indication for surgery. A family history of benign goiter seems to support a benign diagnosis (table I), whereas familial disposition for medullary and papillary thyroid cancer supports a malignant diagnosis (15,16). One patient in the present study was found because her mother had recently been treated for a thyroid tumor containing both a papillary and a medullary carcinoma. The daughter had a papillary carcinoma.

The higher rate of malignant tumors after the age of 60 (fig 1) is probably mainly due to a stricter selection of patients for surgery in this age group. This assumption is supported by the fact that the incidence of surgically excised thyroid nodules in the oldest age group in the present study was only about one third of the corresponding incidence in the group of middle-aged patients, although the prevalence of nodular goiter has been reported to increase with increasing age (17).

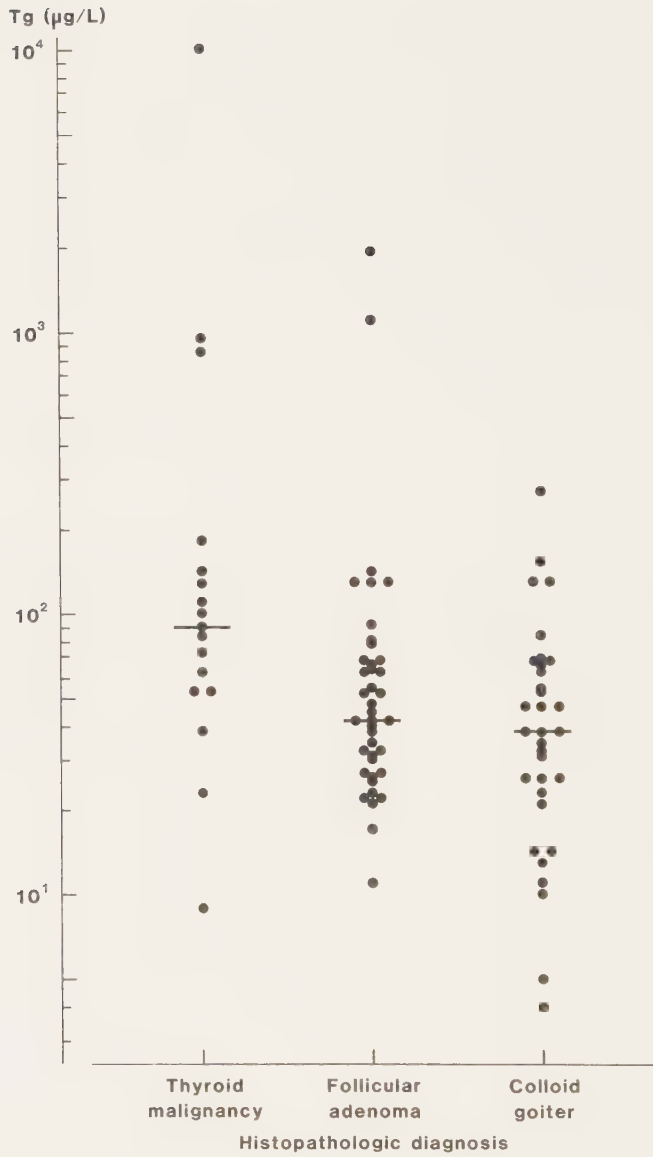


Fig 2: Preoperative serum thyroglobulin (Tg) values in patients with thyroid malignancy, follicular adenoma and colloid goiter. Horizontal lines represent median values.

There is general agreement that malignancy in nodules appearing as solitary and "cold" on scintigram is common with reported rates of 8 to 29 per cent, whereas the contrary is found in nodules shown to be "hot" on scintigram (18). These observations were both supported in the present study. A scintigram showing alternating "cold" and "hot" areas (multiple in table II) is often interpreted as indicating colloid goiter. A malignant tumor is, however, occasionally diagnosed in patients with such a scintigram, namely if the cancer arise in a multinodular goiter or if the cancer is multiple. The frequency of malignancy of 15% in patients in whom the scintigram showed multinodularity (table II) probably reflects the selective nature of the present material rather than the true rate of thyroid cancer in unselected individuals with such a scintigram.

There were no false positive cytologic diagnoses of malignancy in the present study, a finding that is in agreement with statements in other reports (5,6,19). The four cases with a cytologically malignant diagnosis were all papillary carcinomas. Five cases of "histologic" papillary carcinoma were in the present study cytologically classified as "neoplasia NOS". This warrants a comment since the cytologic diagnosis of papillary carcinoma is considered easy in typical cases (11). Histologically three of these tumors had a predominantly follicular growth pattern, and the histologic diagnoses were mainly based upon cellular features (such as occurrence of "ground glass nuclei") in the sections. A fourth papillary carcinoma had a dominant cystic component from which sparse and partly degenerated cellular material was obtained. In the fifth case the aspiration biopsy appeared to have been obtained from an oxyphil adenoma, which was in fact more prominent than the adjacent smaller papillary carcinoma.

It is often impossible for the cytologist to differentiate between follicular carcinoma and adenoma since the essential diagnostic criteria are here related to the capsular and/or vascular invasion of the tumor. Thyroid nodules with a cytologic appearance of follicular tumor (designated "neoplasia" in table III) should therefore be excised for histopathologic examination.

A cytologic diagnosis of neoplasia was in accordance with a histopathologic diagnosis of neoplasia in all cases except four, histologically diagnosed as colloid goiter (11%, table III). In two of these cases, however, the histologic diagnosis was considered uncertain (hyperplastic nodule in colloid goiter or true adenoma).

It has been shown that the cytologic diagnosis is benign (colloid goiter or thyroiditis) in the great majority of unselected individuals with a palpable solitary thyroid nodule (2). A high accuracy of a benign cytologic diagnosis would thus be of great importance since many cases of excisional biopsy might then be avoided. It may be difficult in cytologic (as well as in histopathologic) diagnostics to separate cases of follicular adenoma from cases of colloid goiter (11,20). This was reflected in the present study in the following ways: First, one third of the cases presented as "neoplasia NOS" in table III were interpreted as consistent with a diagnosis of neoplasia but the diagnosis was not certain. Secondly, there was an initial interobserver variation in some ten cases concerning the cytologic distinction between colloid goiter and neoplasia. This variation occurred only in cases with a final diagnosis of adenoma or colloid goiter, while the agreement on the cytologic classification was complete in all 18 cases of malignant tumor. Thirdly, 14 patients with a cytologic diagnosis of colloid goiter had a histologic diagnosis of adenoma. In six of these patients, the histologic diagnosis was considered uncertain (colloid goiter or true adenoma), and another five cases were macrofollicular adenomas with abundant colloid and cystic degeneration. One patient with a benign cytologic diagnosis had a papillary carcinoma but the index nodule did not, in this particular case, correspond to the underlying carcinoma. It thus seems reasonable to conclude in agreement with other authors (6,9,10), that the accuracy of a benign cytologic diagnosis in predicting a benign histopathologic diagnosis is high provided the cytologic aspirate is representative of the underlying pathologic change.

In recent years an increasing number of reports has appeared on the use of serum thyroglobulin in the follow-up of patients with thyroid carcinoma (21-23), whereas only little has been published on the diagnostic benefit

of this test. Contrary to Schneider et al (24), we found that the Tg values were significantly higher in patients with thyroid cancer than in those with benign disorders. The predictive value of the test was, however, low. Tg values above 500 $\mu\text{g/l}$ were only present in patients with either thyroid cancer or thyrotoxicosis. A considerably elevated Tg value in patients with an atoxic solitary thyroid nodule therefore seems to support a diagnosis of thyroid cancer.

CONCLUSIONS

The following parameters were considered useful in the management of patients with a solitary thyroid nodule:

- familial disposition for benign goiter supports a benign diagnosis whereas a family history of thyroid cancer supports a malignant diagnosis.
- a nodule hard by palpation is more often malignant than benign.
- a thyroid scan showing that the nodule is "hot" indicates a benign diagnosis.
- a cytologic diagnosis of malignant tumor is reliable and considered a sufficient basis for definitive surgery for thyroid cancer.
- a cytologic diagnosis of neoplasia almost always indicates a malignant tumor or a follicular adenoma. Such a diagnosis should lead to excisional biopsy.
- the reliability of a benign cytologic diagnosis (colloid goiter or thyroiditis) is high provided the cytologic sample is representative of the underlying pathologic change.
- a considerably elevated serum thyroglobulin value in euthyroid patients supports a malignant diagnosis.

Acknowledgements

We are sincerely indebted to Otto Ljungberg, M.D. at the Department of Pathology for performing the histopathologic revision.

References

1. Vander JB, Gaston EA, Dawber TR. Significance of solitary nontoxic thyroid nodules. Preliminary report. *N Engl J Med* 1954; 251:970-973.
2. Borup Christensen S, Ericsson UB, Janzon L, Tibblin S, Trelle E. The prevalence of thyroid disorders in a middle-aged female population, with special reference to the solitary thyroid nodule. Submitted for publication.
3. Maruchi N, Furihata R, Makiuchi M. Population surveys on the prevalence of thyroid cancer in a non-endemic region, Nagano, Japan. *Int J Cancer* 1971; 7:575-583.
4. Borup Christensen S, Ljungberg O, Tibblin S. Thyroid carcinoma in Malmö 1960-1977. Epidemiological, clinical and prognostic findings in a defined urban population. *Cancer* (in press).
5. Einhorn J, Franzén S. Thin-needle biopsy in the diagnosis of thyroid disease. *Acta Radiol* 1962; 58:321-336.
6. Löwhagen T, Granberg PO, Lundell G, Skinnari P, Sundblad R, Willems JS. Aspiration biopsy cytology (ABC) in nodules of the thyroid suspected to be malignant. *Surg Clin North Am* 1979; 59:3-18.
7. Hamberger B, Gharib H, Melton LJ, Goellner JR, Zinsmeister AR. Fine-needle aspiration biopsy of thyroid nodules. Impact on thyroid practice and cost of care. *Am J Med* 1982; 73:381-384.
8. Miller JM, Hamburger JI, Kini S. Diagnosis of thyroid nodules. Use of fine-needle aspiration and needle biopsy. *JAMA* 1979; 241:481-484.
9. Rosen IB, Wallace C, Strawbridge HG, Walfish PG. Reevaluation of needle aspiration cytology in detection of thyroid cancer. *Surgery* 1981; 90: 747-756.
10. Schwartz AE, Nieburgs HE, Davies TF, Gilbert PL, Friedman EW. The place of fine needle biopsy in the diagnosis of nodules of the thyroid. *Surg Gynecol Obstet* 1982; 155:54-58.
11. Droese M. Aspirationszytologie der Schilddrüse. FK Schattauer Verlag, Stuttgart 1979.
12. Löwhagen T. Thyroid. In: Monographs in clinical cytology. (Ed Wied GL). Aspiration biopsy cytology. Part 1. Cytology of supradiaphragmatic organs (Zajicek J). S Karger, Basel, 1974.

13. Van Herle A, Uller RP, Matthews NL, Brown J. Radioimmunoassay for measurement of thyroglobulin in human serum. *J Clin Invest* 1973; 52: 1320-1327.
14. Hedinger C, Sobin LH et al. Histological typing of thyroid tumours. International histological classification of tumours, No. 11. Geneva: WHO 1974:17-24.
15. Ljungberg O. On medullary carcinoma of the thyroid. *Acta Path Microbiol Scand Section A* 1972, Suppl 231:1-57.
16. Lote K, Anderssen K, Nordal E, Brenhovd IO. Familial occurrence of papillary thyroid carcinoma. *Cancer* 1980; 46:1291-1297.
17. Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA. The spectrum of thyroid disease in a community: The Wickham survey. *Clin Endocrin* 1977; 7:481-493.
18. Ashcraft MW, Van Herle AJ. Management of thyroid nodules. II: Scanning techniques, thyroid suppressive therapy, and fine-needle aspiration. *Head and Neck Surgery* 1981; 3:297-322.
19. Walfish PG, Hazani E, Strawbridge HTG, Miskin M, Rosen IB. Combined ultrasound and needle aspiration cytology in the assessment and management of hypofunctioning thyroid nodule. *Ann Int Med* 1977; 87:270-274.
20. LoGerfo P, Colacchio T, Caushaj F, Weber C, Feind C. Comparison of fine-needle and coarse-needle biopsies in evaluating thyroid nodules. *Surgery* 1982; 92:835-838.
21. Colacchio TA, LoGerfo P, Colacchio DA, Feind C. Radioiodine total body scan versus serum thyroglobulin levels in follow-up of patients with thyroid cancer. *Surgery* 1982; 91:42-45.
22. LoGerfo P, Colacchio D, Stillman T, Feind C. Serum thyroglobulin and recurrent thyroid cancer. *Lancet* 1977; ii:881-882.
23. Barsano CP, Skosey C, DeGroot LJ, Refetoff S. Serum thyroglobulin in the management of patients with thyroid cancer. *Arch Intern Med* 1982; 142:763-767.
24. Schneider AB, Favus MJ, Stachura ME, Arnold JE, Ryo UY, Pinsky S, Colman M, Arnold MJ, Frohman LA. Plasma thyroglobulin in detecting thyroid carcinoma after childhood head and neck irradiation. *Ann Int Med* 1977; 34:29-34.

III

Thyroid carcinoma in Malmö 1960-1977.

Epidemiological, clinical and prognostic
findings in a defined urban population.

S Borup Christensen, O Ljungberg and S Tibblin

Abstract

104 cases of clinically significant thyroid carcinoma (TC) occurred in a demographically well-defined area with, on an average, 243,000 inhabitants, during an 18-year period, corresponding to a yearly incidence of 2.4/100,000. During the later years of the study there was an increase of the age-standardized incidence of differentiated TC. The reason for this is suggested to be a greater health awareness, because only the number of tumors with less advanced growth increased. Sixty-one patients had, as the only presenting sign, a solitary thyroid nodule, while 24 had obviously malignant disease. All cases were revised histologically. Sixty-six patients were found to have papillary carcinoma, whereas 22 cases were diagnosed as follicular, four as medullary and twelve as anaplastic. The prognosis, as estimated by the life table method, was worst for patients with anaplastic cancer followed by follicular, papillary and medullary. Within the papillary group, patients with occult cancer (*i.e.* thyroid tumor not larger than 1.5 cm) and intrathyroidal cancer (*i.e.* thyroid tumor larger than 1.5 cm but not penetrating the thyroid capsule) had a cumulated survival rate not significantly different from the expected rate, and only one of the 46 patients belonging to these two subgroups died from TC.

Introduction

Thyroid carcinoma (TC) constitutes only about one per cent of all malignant tumors reported (1). Numerous reports about factors bearing on prognosis have been published, but the results of such studies are often conflicting. This may partly be due to patient selection caused by skewed age- and sex-distribution (2), accumulation of more advanced cases to special thyroid- or oncologic centers (3), and variations in pathological methodology and classification and registration (4). Therefore, when evaluating qualities such as clinical symptoms and signs, histopathology and prognosis, and making comparisons to other areas, it is important that the patient-materials are representative of the general population.

The aim of the present investigation was to gain further information about factors influencing the prognosis of TC by studying the clinical picture and pathology of such cases in a demographically well-defined population.

POPULATION AND HEALTH SERVICE

Malmö is an industrial, coastal city in the southern part of Sweden. There were, on an average, 243,000 inhabitants during the period of investigation. The population is mainly urban but a minor part, living in the neighbouring districts, is originally rural (5). Goiter is considered non-endemic to the area (6). The age distribution (an average from 1960 to 1977) was very close to the distribution for the Swedish population as a whole in 1970. The female part of the population was 51.8% compared to 50.3% for the whole nation (1). The trend in the development of the population in the area is illustrated in figure 1. During the entire period the number of individuals of 60 years of age or more increased by about 20,000 or 58%, while changes in other age groups generally followed changes in the total population. There is only one general hospital in the city and all diagnostic procedures, treatments, and follow-up of TC are carried out at this hospital. The autopsy frequency was high during the years studied. Thus, in 1969 71.3% of all deceased in the municipality were autopsied (5).

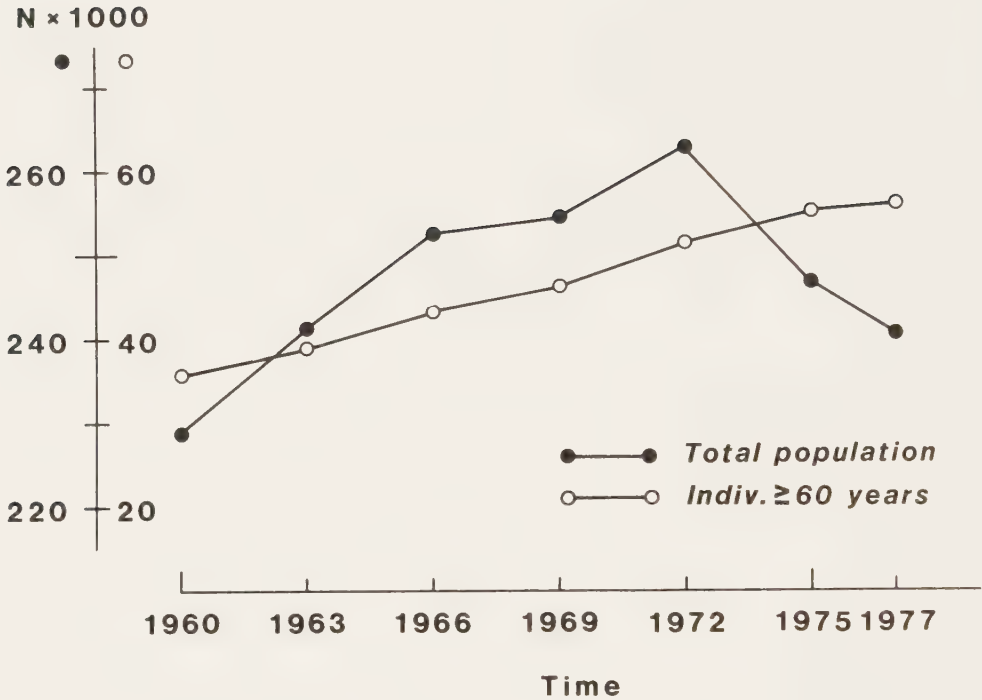


Fig 1: Population development in Malmö 1960 - 1977.

Material

During the 18-year period of investigation, the diagnosis of TC was histologically confirmed in 210 individuals residing in Malmö (figure 2). In 120 of these cases, the histologic diagnosis was based on surgical specimens and in 90, on autopsy material. In 28 cases TC was considered the primary (25 cases) or a contributory (three cases) cause of death. In ten of these the TC was suspected *intra vitam*. Thus, clinical TC was found in 130 individuals. The histopathological material was reviewed. After revision, 104 cases, diagnosed as TC, were included in the study, whereas 26 were excluded. Twenty-three of the excluded cases belonged to the group surgically treated and the revised diagnosis was, in most cases, benign follicular adenoma. Three autopsy cases were excluded from the study because,

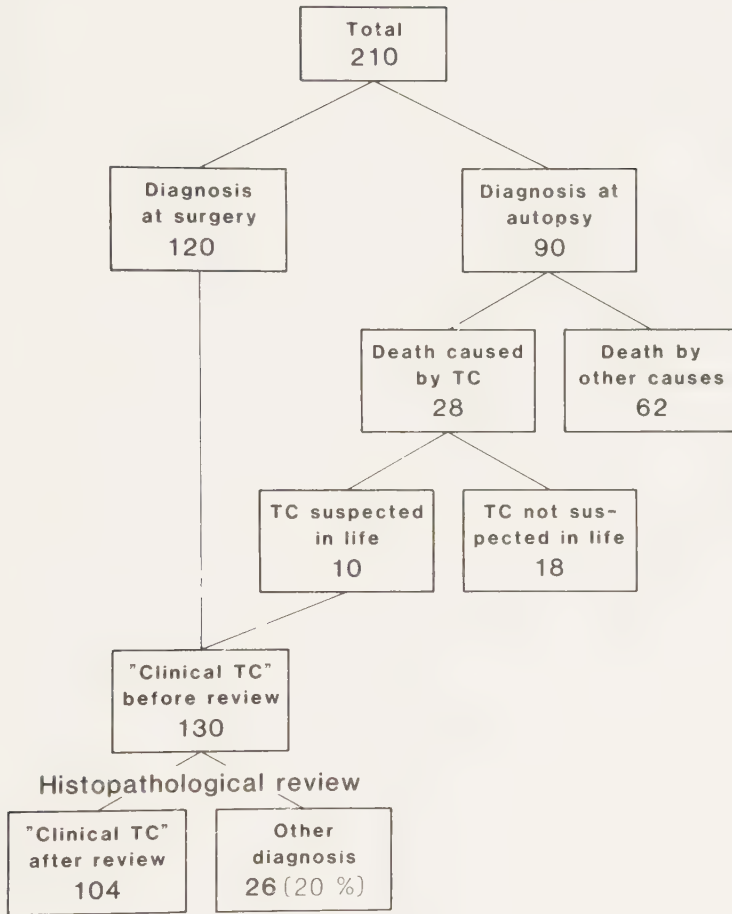


Fig 2: New cases of histopathologically diagnosed thyroid carcinoma in Malmö 1960-1977.

at histological review, the thyroid tumors were interpreted as metastases from other malignant tumors. In 62 of the autopsy cases the TC diagnosis was a "side finding" not related to the cause of death. This corresponds to an autopsy prevalence of 0.18%. The pathological findings in these cases are given in Table I.

Histopathologic types	N	Regional metast	Distant metast	Tumor size (cm)
Papillary	39	3	0	0.3 - 2
Follicular	16	0	2	0.5 - 4
Medullary	7	0	0	0.5 - 3

Table I: Side findings of thyroid carcinoma at 30 892 routine autopsies in Malmö 1960-1977. TC not cause of death. N = 62.

Definitions and Methods

Clinical TC was defined as histologically confirmed TC, diagnosed or suspected in living patients. The histopathological classification was made according to WHO 1974 (7). Only malignant epithelial tumors were included in the study. Cancers exclusively composed of oxyphil cells (Askanazy cells) were included within the group of follicular carcinoma. Tumors primarily diagnosed as small cell anaplastic carcinomas were considered as malignant lymphomas and were excluded. "Occult cancer" was defined as a thyroid tumor not more than 1.5 cm in its largest diameter, "intrathyroidal cancer" as a cancer larger than 1.5 cm in its largest diameter and not breaking through the thyroid capsule, and "extrathyroidal cancer" as a thyroid cancer more than 1.5 cm in largest diameter and with evidence of penetration of the thyroid capsule. These definitions were used regardless whether or not metastases were present. When the site of a histopathologically diagnosed carcinoma did not correspond to the palpation finding leading to surgery, the cancer was further designed as "incidental".

Information about history, symptoms and signs, diagnostic results and treatment were collected retrospectively from hospital records. Thyroid scintigraphy and fine-needle aspiration cytology were available during the entire period. During the first part of the period, thyroid scan was performed with

^{131}I ; later ^{99}Tc -pertechnetate was used. Age-specific incidence rates were calculated on the basis of the average number of individuals in Malmö in the corresponding age-interval and time-period. Crude (non age-specific) incidence rates were standardized for age to the Swedish population in 1970 and estimated by the direct method (8). All incidences are given per 100,000 persons and year.

The investigation period was divided into three parts, each of six years: Period I 1960-1965, period II 1966-1971, and period III 1972-1977.

STATISTICAL METHODS

Survival was estimated according to the life table method (9). Figures for expected survival were calculated using information on the mortality rate for the Malmö population 1970-1974 (10). Relative survival rate is defined as the ratio between the observed survival rate and the expected survival rate (11). In estimation of standard error for the cumulated survival rates, Greenwoods formula was used (12). Ninety-five per cent confidence limits and statistical differences between survival rates were calculated according to Colton (12). Incidence was considered to follow a Poisson distribution, and tests of statistical differences between incidence density rates were made according to Cox (13). In other statistical calculations the chi square test was used.

The observation period was counted from the time of diagnosis (suspected diagnosis concerning the autopsy cases) to death, lost to follow-up, or the closing date of the study, December 31, 1979. The observation time was approximated to the number of whole years. Patients followed personally all had a clinical examination, chest X-ray and laboratory screening. Patients examined elsewhere generally had a clinical examination with a laboratory screening once or twice a year and chest X-ray once a year or every two years depending on the time interval from the diagnosis.



Fig 3: Age- and sex distribution and age-specific incidence in 104 patients with thyroid carcinoma in Malmö 1960-1977.

Results

INCIDENCE, AGE AND SEX

The average incidence of clinical TC in Malmö for the period 1960-1977 was 2.4. The figure for females was 3.4, for males 1.3. The ratio between men and women was 1:2.9. The age range was 15 to 89 years. Age distribution and the age-specific incidences are recorded in figure 3. The age standardized incidence in period III was significantly higher than in period II but not significantly different from that in period I. Excluding cases of anaplastic carcinoma (twelve cases), there was a significant difference also between period III and I as regards age standardized incidence ($p < 0.05$, table II).

Table II: Age-standardized incidence of differentiated thyroid carcinoma in Malmö 1960-1977.

	Period I 1960-1965 n = 26	Period II 1966-1971 n = 24	Period III 1972-1977 n = 42	Total 1960-1977 n = 92
Age-standardized incidence	1.8	1.6	2.7 ¹⁾	2.0

1) $p < 0.05$ in relation to period I and II

PATIENT HISTORY, SYMPTOMS AND SIGNS

Twenty-eight persons had a family history of goiter. One parent of each of three patients had had a papillary or anaplastic TC. All three parents were also patients in the present study. In seven cases radiation therapy had been given to the neck 12-40 years earlier. Seven patients had been surgically treated for benign goiter 1-28 years before the present attendance. Specimens from these operations were re-examined and, in one case, a TC of the same type as at the present operation was revealed. Twenty-two patients had a history of goiter for more than three years, nine for more

than ten years. The presenting symptoms are recorded in table III.

Table III: Presenting symptoms in 104 patients with thyroid cancer in Malmö 1960-1977.

Presenting symptom	Period I 1960-1965 n = 33	Period II 1966-1971 n = 24	Period III 1972-1977 n = 47	Total 1960-1977 n = 104
Thyroid lump as only finding. () Incidental, clinical finding	19 (3)	13 (6)	37 ¹⁾ (16 ¹⁾)	69 (25)
Symptoms caused by advanced tumor growth and/or metastases	12	10	9	31
Symptoms of thyro- toxicosis or hyper- parathyroidism	2	1	1	4

1) $p < 0.05$

Sixty-nine had a thyroid lump as the only symptom, and of these, 25 were discovered incidentally at clinical screening or on clinical examination for other complaints. Thirty-one persons came under medical care because of symptoms of advanced local tumor growth or of metastases. Four tumors were incidental histopathological findings at surgery for thyrotoxicosis and hyperparathyroidism. A thyroid lump was the only presenting symptom in 79% of the cases in period III; in period II the corresponding figure was 54% and in period I 58%. The difference between the periods was significant ($p < 0.05$). The number of incidentally discovered thyroid lumps was also larger in period III than in the other periods ($p < 0.05$).

The other presenting symptoms shown in table II did not change significantly during the years studied.

CLINICAL EVALUATION

On clinical examination, the malignant diagnosis was strongly suspected or obvious in 24 patients: five had a rapidly growing goiter, four had goiter and node metastases, six had node metastases only, and nine had distant metastases. Sixty-one patients had a solitary thyroid lump as the only sign, whereas 18 showed diffuse or multinodular goiter. One patient presented with hyperparathyroidism. Thyroid scan was performed in 78 cases. In 57 (71%) there was a "solitary cold spot" on the scintigram, in the remaining cases the scintigram was normal (eight cases) or indicated a multinodular goiter (13 cases). Fine-needle aspiration was carried out in 72 patients. In 40 of these (56%) the cytology report indicated malignancy, in 28 cases follicular tumor or colloid goiter and in four the cytological material was not evaluable. The diagnostic results of the clinical examination, thyroid scan and thyroid cytology are presented in table IV.

Table IV: Diagnosis based upon clinical, scintigraphical and cytological findings in 104 patients with histopathologically proven thyroid carcinoma in Malmö 1960-1977.

Cancer	38
Suspicion of cancer	26
Solitary nodule	26
Multinodular goiter	10
Miscellaneous	4

SURGICAL TREATMENT

Ninety-seven patients were subjected to surgical treatment or biopsy. Thirty had a total thyroidectomy, 30 a lobectomy, 17 a lobectomy with a partial resection of the opposite lobe, six a bilateral resection and seven a unilateral resection. In seven cases the only operative intervention was a surgical biopsy. The surgical procedure was considered palliative in twelve cases, which means that 78 patients were considered to have had a curative operation. A more thorough evaluation of the surgical treatment is reported elsewhere (14).

NON-SURGICAL TREATMENT

Thyroxine treatment was given in a dose of 0.1 - 0.3 mg/day. Nine patients had ¹³¹I-treatment for metastases, 13 had external radiological therapy, and cytostatic drugs were given to four.

HISTOPATHOLOGY

The histopathological findings are given in table V. In the papillary group, node metastases were significantly more frequent among patients with extra-thyroidal tumors than among patients with intrathyroidal and occult tumors ($p < 0.01$). Nine of the 22 follicular carcinomas were of Askanazy cell type, and among them, two contained papillary structures. The twelve cases of anaplastic carcinoma were all of the giant cell type. The four medullary carcinomas were solitary and apparently non-familial. In one of these, two microscopic papillary carcinomas were demonstrated besides the medullary carcinoma.

The mean age at diagnosis was 49 years for papillary cancer, 53 for follicular cancer, 55 for medullary cancer, and 75 for anaplastic cancer. Within the papillary group, patients with occult and intrathyroidal tumors had a mean age of 45 years, whereas the corresponding figure for patients with extrathyroidal growth was 56 years.

Thirteen of the 25 occult tumors were incidental findings at operation, six were palpable, five presented with node metastases and one with bone

metastases. Among the intrathyroidal tumors, one was an incidental finding at operation (in a patient operated for thyrotoxicosis), while none of the extrathyroidal carcinomas were incidental findings.

Table V: The distribution of histopathological types by size and extension of the primary tumor in 104 patients with thyroid carcinoma in Malmö 1960-1977.

Tumor extension	Papillary n = 66	Follicular n = 22	Medullary n = 4	Anaplastic n = 12	N 104
Occult	23	1	1	0	25
Intrathyroidal	23	14	3	0	40
Extrathyroidal	20	7	0	12	39
Positive nodes	29 ¹⁾	2	0	6	37
Distant metastases	1 ²⁾	4 ³⁾	0	10	15
1) Occult 7 Intrathyroidal 7 Extrathyroidal 15 2) From occult TC 3) Intrathyroidal 2 Extrathyroidal 2					

The distribution of differentiated TC by tumor size and extension during the period of the study is shown in table VI. In period III, intrathyroidal tumors were significantly more frequent than in the other periods ($p < 0.01$). The incidence of occult and extrathyroidal cancers did not differ significantly between the periods. Anaplastic cancer only occurred in periods I and III (seven and five cases respectively). The relative distribution of the histopathological types did not change significantly during the years studied.

Table VI: The distribution of thyroid carcinoma in Malmö 1960-1977
by size and extension of primary tumor.

Tumor extension	Period I 1960-1965 n = 26	Period II 1966-1971 n = 24	Period III 1972-1977 n = 42	Total 1960-1977 n = 92
Occult	7	9	9	25
Intrathyroidal	9	9	22 ¹⁾	40
Extrathyroidal	10	6	11	27

1) Incidence significantly increased in relation to
period I and II ($p < 0.01$)

FOLLOW-UP

On the closing date of the follow-up, December 31, 1979, 34 patients were found to have died. Of the remaining patients, 38 were examined by one of us, whereas clinical information about 32 patients was collected by review of hospital records (27 cases) or by inquiry made by the physician responsible for the TC follow-up (five cases). One woman could be followed for four years only. She was included in the study as a 4-year control. Autopsy was performed in 32 of the 34 deceased patients.

The result of the follow-up is presented in table VII. The cause of death in one of the eleven patients, who had died without recurrence, was pulmonary fibrosis, probably caused by external radiation therapy to the mediastinum given for recurrent node metastases; none of the other ten deaths were related to TC. In one of the five patients, who died from other causes with recurrent TC, the recurrence was diagnosed *intra vitam*; in the other four cases the autopsy finding was incidental, unrelated to the cause of death. The observed and expected survival rates for all 104 patients are shown in figure 4. The curve for observed survival has one marked "dip" after the first year (caused by death from anaplastic TC). After the seventh year of observation, the distance between the curves does not increase, indicating that the observed survival rate after this point is not below the expected rate.

Table VII: Results at the follow-up, December 31, 1979, in 104 patients with clinical TC diagnosed in Malmö 1960-1977.

	Papillary n=66	Follicular n=22	Medullary n=4	Anaplastic n=12	Total n=104
Alive without recurrence	49	10	3	0	62
Dead without recurrence	7	3	1	0	11 ¹⁾
Alive with recurrence	3	5	0	0	8
Dead from other cause with TC recurrence	4	1	0	0	5
Death caused by TC	3 (5%)	3 (14%)	0 (0%)	12 (100%)	18(17%)

1) Two patients not autopsied

Papillary cancer

The relative survival rate for patients with papillary cancer was lowest eight years after diagnosis (fig 5). No deaths from TC occurred after this point. The survival rate was significantly lower than expected after five years after presentation ($p < 0.05$). The survival rate for patients with occult and intrathyroidal cancers was not lower than expected at any point (fig 6). One woman with occult cancer and node metastases died from TC four years after presentation. In another woman with intrathyroidal TC, a spot on the right lung, 1 cm in diameter, was found by X-ray ten years after the TC diagnosis. This spot did not increase in size during the following nine years of observation. None of the other 44 patients with occult or intrathyroidal tumors had recurrence or died from TC. The survival rate among the 20 patients with extrathyroidal growth was significantly lower

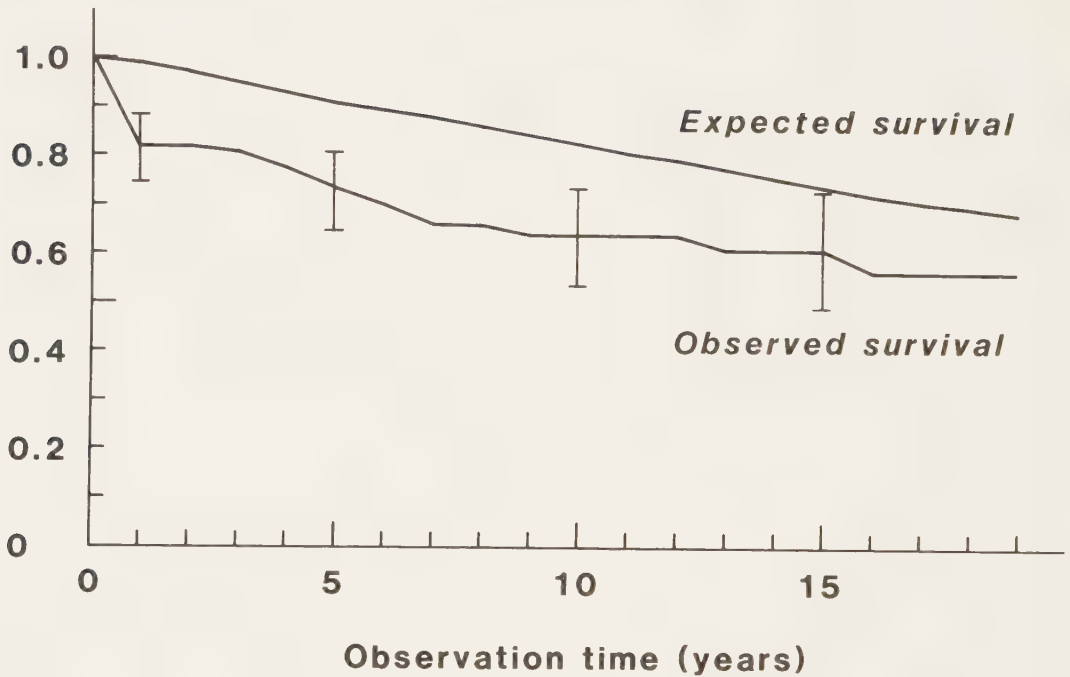
Survival rate

Fig 4: Cumulated survival rate with 95% confidence limits in 104 patients with thyroid carcinoma related to expected survival rate for a corresponding group of individuals.

than expected after the fifth year ($p < 0.05$). Two patients from this group died from TC, and two died postoperatively having residual TC at autopsy. Four patients were found to have recurrence; two of these had died from unrelated causes, whereas two were alive and in good condition three and six years after diagnosis.

Dividing patients with papillary cancer into two age groups, one group of 25 patients aged below 40 and one group of 41 patients aged above 40, the younger patients had a significantly higher survival rate than the older ones five years after diagnosis according to the survival rates ($p < 0.05$).

Survival rate

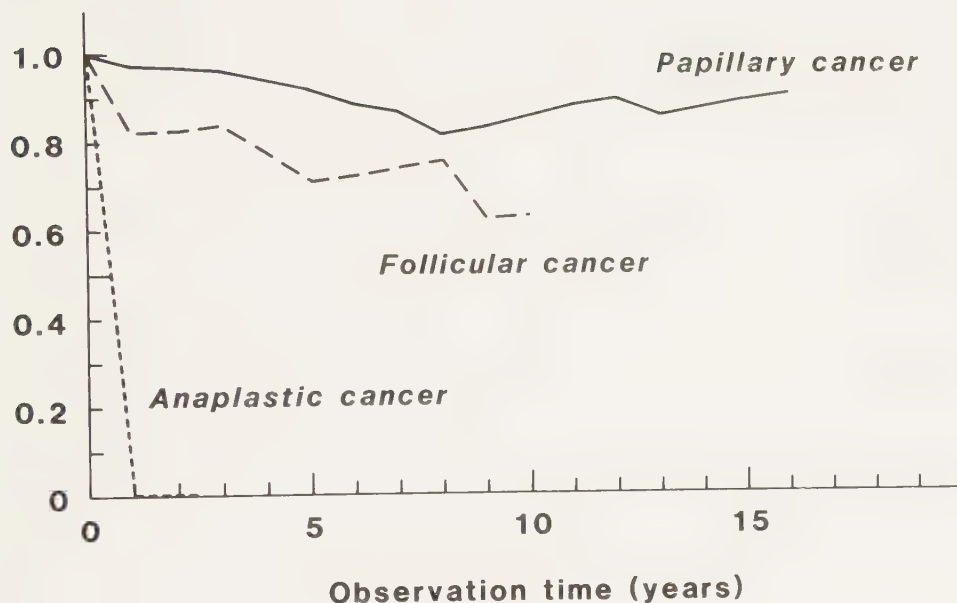


Fig 5: Relative survival rate for patients with papillary TC (n=66), follicular TC (n=22) and anaplastic TC (n=12).

No patient under 40 at presentation died from TC. One had a suspected recurrence, the size of which remained unchanged for nine years. Neither sex nor node status seemed to influence the prognosis significantly as indicated by the survival rates.

Follicular cancer

The relative survival rate for the 22 patients in this group was significantly lower than expected after the first year after diagnosis but not significantly different from the survival rate among patients with papillary cancer (fig 5). Three patients died from TC one to four years after diagnosis (table VII). All three had had extrathyroidal growth at presenta-

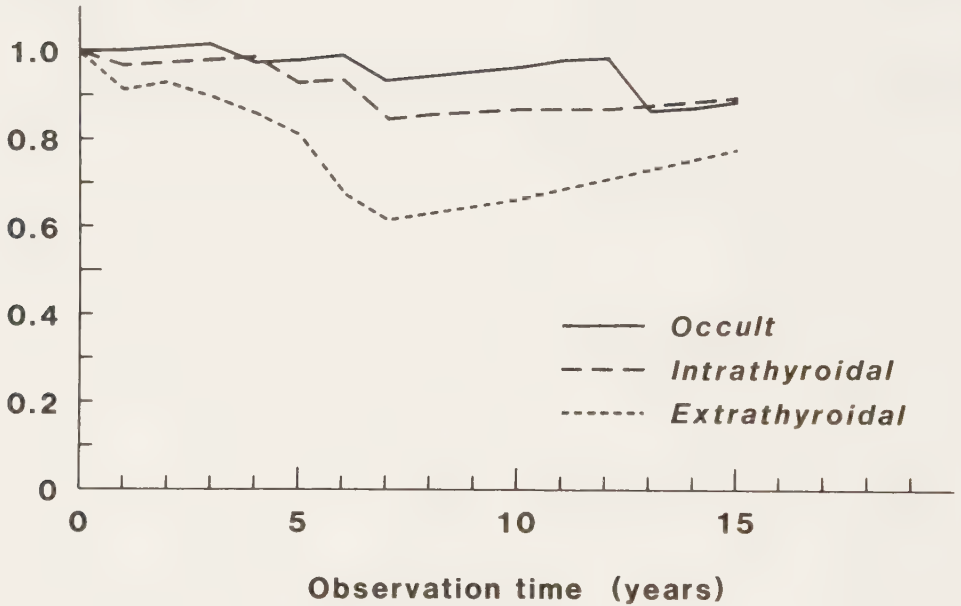
Survival rate

Fig 6: Relative survival rate for patients with occult (n=23), intra-thyroidal (n=23) and extrathyroidal (n=20) papillary TC.

tion. Five patients were alive with recurrent tumor three to nine years after the diagnosis. On operation four of them were found to have intra-thyroidal tumors, one extrathyroidal. One man who died from a stroke nine years after diagnosis was found to have recurrent TC at the autopsy to such an extent that it might have been a contributory cause of death.

Medullary and anaplastic cancer

The four patients with medullary cancer had no signs of recurrence 5 to 16 years after diagnosis indicated by normal calcitonin levels (table VII). The twelve patients with anaplastic cancer all died from TC within one year (fig 5).

Discussion

The population of Malmö has been found suitable for epidemiological studies (15-19). It is demographically well defined and is served by only one general hospital. Concerning cancer diseases one further condition facilitates such studies, *i.e.* the fact that in Sweden all cancer cases are notifiable to the National Cancer Registry.

The patients in the present investigation are considered to constitute all new cases of clinical thyroid cancer in Malmö during the period 1960-1977. Information from the Swedish Cancer Registry on thyroid cancer in the community of Malmö was available for the period 1960 through 1974. This information was checked with the diagnoses recorded in the registries at the Departments of Pathology, Surgery and ENT. Only two patients with verified clinical TC were not recorded in the Swedish Cancer Registry, which indicates that the reporting system has been effective. In the ten patients with "TC suspected in life" (fig 2) the diagnosis was not histopathologically confirmed until autopsy. All of them had a suggested TC diagnosis *ante mortem* on the basis of clinical signs and/or cytology findings. The 18 patients, where TC was not clinically suspected *intra vitam* had disseminated malignant disease at autopsy. Askanazy cell carcinomas, even those with a papillary component (two cases) were included within the group of follicular cancer, because biologically they are considered to be more closely related to follicular than to papillary carcinoma (20).

Most incidence figures on TC in literature are based on information from central registries (21,22). Provided that the reporting systems are effective, such figures will often be an overestimation of the true incidence of clinical, significant TC for two reasons: firstly, incidental autopsy findings are included; secondly, histopathological review will change many diagnoses from cancer to benign lesions, as recently shown by Saxén et al (23) and confirmed in the present study (fig 2). Thus the age standardized incidence of TC in Sweden 1960 - 1977 was 3.6/100,000 person-years on an average according to the Cancer Registry (1) compared to the 2.4 in the

present study. The incidence for all Sweden in 1960 has been estimated by Franssila et al (24). Following histopathological review and exclusion of autopsy cases the figure became 1.8/100,000 person-years, which corresponds rather well to our average figure of 1.95 for the 1960s. The increased incidence of about 33% (table II) in Malmö during the 1970s, seems to be in correspondence with a rising incidence in all Sweden, even though the increase was not as pronounced as in Malmö. Thus, the difference in age standardized incidence between 1960 and 1977 in all Sweden was 22% (1). The decrease in incidence after the age of 80 (fig 3) can probably be explained by the fact that patients with clinical disease at that age are less likely to have surgery, and with it, an accurate diagnosis during life. An additional explanation could be that the autopsy rate decreased in Malmö in the oldest age group (5).

The age standardized incidence of differentiated TC was on a higher level during the last years of the study (period III) than during the first twelve years (period I and II). One explanation could be that more TC cases with minor symptoms and less advanced tumor growth were diagnosed during life because of greater health consciousness among patients as well as physicians and increased availability of medical care. The fact that TC prevalence in the population is probably considerably higher than the annual incidence (25) paves the way for such a possibility. In the present study the explanation mentioned above is supported by the following facts: firstly, the proportion of patients with a thyroid lump as the only sign of TC increased in period III; secondly, thyroid lumps diagnosed incidentally in patients consulting doctors for other complaints were more frequent in period III; thirdly, the incidence of intrathyroidal cancer was higher during the last six years of the study, while the incidence of more advanced tumors and occult cancer remained unchanged during the years studied. Another possible explanation for the increased incidence of TC of the last period might be a more careful histopathological examination. This would probably implicate detection of more follicular and incidental cancer, since the cancer diagnosis in these cases is strongly dependent on the number of tissue blocks taken for microscopy from each specimen (26,27). However, the relative distribution of the different histopathological types did not change during the years studied, neither did the

number of histopathological, incidental findings increase in period III. Therefore, possible changes in the histopathological procedures are not considered to be the explanation for the increased incidence. In a study from Connecticut (28) a five-fold increase of the TC incidence over a forty-year period was described. The most likely explanation was considered to be radiation therapy to the neck in adolescence and childhood. In the present study, radiation therapy cannot explain the difference in incidence, since only seven persons had been subjected to such treatment. In Olmsted county the incidence of TC increased three-fold from 1935 to 1965 (29). This was considered partly to be due to the same reasons as suggested in the present study, *i.e.* increased clinical awareness of the disease, partly to increased histopathological recognition of occult lesions.

Three patients had a family history of TC. In two cases both parent and offspring had papillary TC, in the third case the mother had anaplastic TC and the daughter follicular TC. In earlier reports, familial occurrence of TC in Gardner's syndrome has been described (30) but more recently, accounts of papillary TC as the only familial manifestation have been published (31,32). Thus there seems to be strong evidence that genetic disposition may be one etiologic factor in the development of papillary TC.

There is general agreement that several factors such as histopathological type, age at presentation, extent of primary tumor and the presence or absence of distant metastases influence the prognosis of TC (2, 33-36). The significance of these factors was also apparent in the present study. In order to assess such factors correctly and to be able to generalize the assessments, it is important that patient-materials are representative of the population. It is often maintained that another condition to be fulfilled is a follow-up period of sufficient length, since death caused by TC is claimed to occur 15 to 25 years after treatment (35,37). However, in such studies it is generally not stated to what extent autopsies have been conducted to confirm TC as the cause of death. In the present study, five of 34 deaths were proven to be caused by metastases from neoplasms other than TC. None died from TC later than six years after presentation. Thus, it seems that death from TC more than 15 years after the diagnosis is unusual and will only marginally affect survival figures as estimated

by the life table method. Besides, the demand for long-time follow-up is in conflict with the demand for representativity, because aged TC-materials may have a deviating composition as to demographic, etiologic, histopathologic and clinical qualities. The fact that the proportion of intrathyroidal tumors increased in the later part of the present study is an example of how patient-materials can change with time. Using the life table method to estimate the survival rate, it is partly possible to compensate for a comparatively brief follow-up time because it enables one to use all survival information on the closing date of the study (11). However, the fact that differentiated TC has a low mortality rate during the first years after diagnosis (fig 5) may implicate that the late entries in the present study, *i.e.* cases with an observation time below five years (15 cases) could lead to a slight overestimation of the survival rate (38). For the same reason it is not advisable to make comparisons between the time periods concerning survival, since a low mortality rate from TC in period III (caused by brief follow-up) would bias such a comparison.

The figures on histopathological distribution, tumor extension and prognosis (with the reservation mentioned above) found in the present study are considered to be representative for an area with a high level of medical care. Only a few studies dealing with TC in demographically well-defined areas have been published. The distribution of TC by histologic type in the Olmstedt-study (29) was found to be very close to that in the present study. Also the prognosis was similar in the both regions: the mortality rate in TC in Olmstedt was approximately 15%, corresponding to the 17% in Malmö (table VII). The prognosis for TC in a Finnish population as reported by Franssila (39) seems to be worse than that found by us in the Malmö area. This may partly be due to a somewhat higher proportion of anaplastic carcinoma and of tumors with extrathyroidal growth. The incidence of different histopathological types in Iceland and N.E. Scotland was examined by Williams et al (40). The proportion of papillary cancer was considerably higher in Iceland than in Scotland and the figures from Scotland seem to agree best with our figures. The high proportion of papillary cancer in Iceland compared to the other Nordic countries has been confirmed by other authors (24). Lindahl has studied papillary cancer in Denmark 1943-1968 (41). One remarkable finding in the Danish study was a sharply increasing

incidence of TC through the years, which might partly be due to better diagnostic possibilities and increased awareness of the disease. Another finding was a notably high crude mortality rate of 29% compared to the crude rate of 5% in the present study (table VII). Partly, the difference of 24% in otherwise comparable populations might be explained by methodological reasons in that relatively more advanced cases were reported because the reporting system in Denmark is on a voluntary basis.

Occult TC appears to be very frequent in thorough autopsy studies (27,42, 43). In Malmö the subject has been studied recently by Bondeson and Ljungberg (44) and a prevalence of 8.6% of TC was found, the great majority being of the papillary type. Since the thyroid gland lies superficially the apparently paradoxical situation can arise that occult tumors are palpable, as node metastases occasionally are palpable. In the present study, six of 25 occult tumors were in fact localized by palpation, six were diagnosed through their metastases while 13 were incidental findings at pathological examination. It has earlier been claimed that occult papillary cancer invariably has a favorable prognosis (45,46) but recent reports have appeared on occasional cases of occult TC of this type with wide-spread disease and poor prognosis (47-49). At the presentation, two of the patients with occult, papillary carcinoma in the present series were inoperable, one because of mediastinal node metastases and one because of distant metastases; the patient with mediastinal metastases died later from TC. None died from TC in the intrathyroidal group and only one had a suspected recurrence. Other authors too, report a similar prognosis for intrathyroidal and occult papillary cancer (36,49), even though an increased tumor size is frequently suggested to correlate with worsened prognosis (2,33). Patients with incidentally discovered occult tumors probably have a favorable prognosis. From a prognostic and clinical point of view, it therefore seems justified to consider those occult papillary carcinomas, not larger than 1.5 cm in diameter, which have been discovered incidentally on pathological examination as a separate group and to include the remaining, clinically discovered occult carcinomas within the groups of intrathyroidal and extrathyroidal carcinomas. Since the number of incidentally discovered follicular carcinomas and medullary carcinomas is small, it is difficult to make an estimation of the prognosis. It seems reason-

able to treat such cases in the same way as clinically discovered carcinomas, until further information is available.

Acknowledgments

We are sincerely indebted to Kaj Lundgren, M.D. at the ENT-department for allowing us to include in the study patients treated at the ENT-department. For skillful statistical guidance we should like to express our sincere gratitude to Jonas Ranstam, B.Sc.

References

1. Cancer incidence in Sweden 1977. National Board of Health and Welfare. The Cancer Registry. Stockholm 1981, p 105, p 108, and p 24.
2. Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP. Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine* 1977;56:171-196.
3. Staunton MD, Skeet RG. Thyroid cancer: Prognosis in 469 patients. *Br J Surg* 1979;66:643-647.
4. Schottenfeld D, Gershman ST. Epidemiology of thyroid cancer. *CA-A Cancer Journal for Clinicians* 1978;28:66-86.
5. Berge T, Lundberg S. Cancer in Malmö 1958-1969. An autopsy study. *Acta Patol Microbiol Scand, Suppl* 260, 1977, pp 13 & 21.
6. Höjer JA. Kropfstudien. *Sv Läkarselskapets handlingar* 1931;57:1-104.
7. Hedinger Chr, Sobin LH, et al. Histological typing of thyroid tumours. International histological classification of tumours, No. 11. Geneva: WHO, 1974;17-24.
8. Fleiss JL. Statistical methods for rates and proportions. New York: Wiley interscience, 1981:244-247.
9. Berkson J, Gage RP. Calculation of survival rates for cancer. *Proc Mayo Clin* 1950;25:270-286.
10. Arwidsson A. Personal communication. Statistiska Centralbyrån, Stockholm 1979.
11. Ederer F, Axtell LM, Cuttler SJ. The relative survival rate: A statistical methodology. *National Cancer Inst. Monographs*, 1961;6:101-121.
12. Colton T, Scd. *Statistics in Medicine*. Boston: Little Brown & Co, 1974: 249.
13. Cox DR. Some simple approximate tests for Poisson variates. *Biometrika* 1953;40:354-360.
14. Christensen Borup S, Ljungberg O, Tibblin S. Surgical treatment of thyroid carcinoma in a defined population 1960-1977. Evaluation of the results after a conservative surgical approach. *Am J Surg*, in press.
15. Isacsson SO. Venous occlusion plethysmography in 55-year-old men. A population study in Malmö, Sweden. *Acta Med Scand* 1972, Suppl 297.

16. Berge T, Ekelund G, Mellner C, Pihl B, Wenckert A. Carcinoma of the colon and rectum in a defined population. *Acta Chir Scand* 1973, Suppl 438.
17. Ekelund G. On colorectal polyps and carcinoma with special reference to their interrelationship. Thesis. Malmö General Hospital, Malmö 1974.
18. Lannerstad O. Död och sjukdom bland medelålders män. Thesis. Malmö General Hospital, Malmö 1978.
19. Lindhagen T. Crohn's disease in a defined population. Results of surgical treatment. Thesis. Malmö General Hospital, Malmö 1982.
20. Li Volsi VA. Pathology of thyroid cancer. In Greenfield LD, ed. *Thyroid cancer*. CRC Press Inc 1978;108.
21. Sancho-Garnier H. L'épidémiologie des cancers de la thyroïde. *Ann Radiol* 1977;20:715-721.
22. Doll R, Muir C, Waterhouse S. Cancer incidence in five continents. Vol III UICC, 1976.
23. Saxén E, Franssila K, Bjarnasson O, Normann T, Ringertz N. Observer variation in histologic classification of thyroid cancer. *Acta Path Microbiol Scand* 1978;86:483-486.
24. Franssila KO, Saxén E, Teppo L, Bjarnasson O, Tullinius H, Normann T, Ringertz N. Incidence of different morphological types of TC in the nordic countries. *Acta Path Microbiol Scand* 1981;89:49-55.
25. Maruchi N, Furihata R, Makiuchi M. Population surveys on the prevalence of thyroid cancer in a non-endemic region, Nagano, Japan. *Int J Cancer* 1971;7:575-583.
26. Lang W, Georgii A, Stauch G, Kienzle E. The differentiation of atypical adenomas and encapsulated follicular carcinomas in the thyroid gland. *Virchows Arch (Pathol Anat)* 1980;385:125-141.
27. Sampson R, Key CR, Buncher CR, Iijima S. Thyroid carcinoma in Hiroshima and Nagasaki. I. Prevalence of thyroid carcinoma at autopsy. *JAMA* 1969; 209:65-70.
28. Pottern LM, Stone BJ, Day NE, Pickle LW, Fraumeni Jr JF. Thyroid cancer in Connecticut 1935-1975: An analysis by cell type. *Am J Epidemiol* 1980; 112:764-774.
29. Verby JE, Woolner LB, Nobrega FT, Kurland LT, McConahey WM. Thyroid cancer in Olmstedt county 1935-1965. *J Natl Cancer Inst* 1969;43:813-820.

30. Camiel MR, Mulé JE, Alexander LL, Benninghoff DL. Association of thyroid carcinoma with Gardner's syndrome in siblings. *N Engl J Med* 1968;278:1056-1058.
31. Lote K, Anderssen K, Nordal E, Brenhovd IO. Familial occurrence of papillary thyroid carcinoma. *Cancer* 1980;46:1291-1297.
32. Phade VR, Lawrence WR, Max MH. Familial papillary carcinoma of the thyroid. *Arch Surg* 1981;116:836-837.
33. Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR. Classification and prognosis of thyroid carcinoma. A study of 885 cases observed in a thirty year period. *Am J Surg* 1961;102:354-387.
34. McKenzie A. The natural history of thyroid cancer. A report of 102 cases analyzed 10-15 years after diagnosis. *Arch Surg* 1971;102:274-277.
35. Cady B, Sedgwich CE, Meissner WA, Bookwalter JR, Romagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. *Ann Surg* 1976;184:541-553.
36. Beaugié JM, Brown CL, Doniach I, Richardson JE. Primary malignant tumors of the thyroid: the relationship between histological classification and clinical behavior. *Br J Surg* 1976;63:173-181.
37. Tollefsen HR, DeCosse JJ, Hutter RVP. Papillary carcinoma of the thyroid. A clinical and pathological study of 70 fatal cases. *Cancer* 1964;17:1035-1044.
38. Heise H. The effect of a temporary change in survival on the life table method for computing survival rates. Methodological note No 8, End results, Evaluation section, National Cancer Institute, February 1959.
39. Franssila KO. Prognosis in thyroid carcinoma. *Cancer* 1975;36:1138-1146.
40. Williams ED, Path MRC, Doniach I, Path FRC, Bjarnasson O, Michie W. Thyroid cancer in an iodine rich area. A histopathological study. *Cancer* 1977;39:215-222.
41. Lindahl F. Papillary thyroid carcinoma in Denmark, 1943-1968. *Cancer* 1975;36:540-552.
42. Fukunaga FH, Yatani R. Geographic pathology of occult thyroid carcinomas. *Cancer* 1975;36:1095-1099.
43. Sampson R, Woolner LB, Bahn RC, Kurland LT. Occult thyroid carcinoma in Olmstedt, Minnesota: prevalence at autopsy compared with that in Hiroshima and Nagasaki, Japan. *Cancer* 1974;34:2072-2076.

44. Bondeson L, Ljungberg O. Occult thyroid carcinoma at autopsy in Malmö, Sweden. *Cancer* 1981;47:319-323.
45. Woolner LB, Lemmon ML, Beahrs OH, Black BM, Keating FR. Occult papillary carcinoma of the thyroid gland: a study of 140 cases observed in a 30-year period. *J Clin Endocrinol* 1960;20:89-105.
46. Hubert JP, Kiernan PD, Beahrs OH, McConahey WM, Woolner LB. Occult papillary carcinoma of the thyroid. *Arch Surg* 1980;115:394-398.
47. Fraumeni CM, Patchefsky AS, Cobanoglu A. Thyroid carcinoma. A clinical and pathological study of 125 cases. *Cancer* 1979;43:2414-2421.
48. Patchefsky AS, Keller IB, Mansfield CM. Solitary vertebral column metastases from occult sclerosing carcinoma of the thyroid gland: Report of a case. *Am J Clin Pathol* 1970;53:596-601.
49. Franssila KO. Outcome in papillary carcinoma of the thyroid. *Ann Chir Gynaecol* 1978;67:49-57.

IV

Surgical treatment of thyroid carcinoma in a defined population 1960 - 1977.

Evaluation of the results after a
conservative surgical approach

S Borup Christensen, O Ljungberg and S Tibblin

Abstract

Ninety patients from a demographically well-defined area of, on an average, 243,000 inhabitants were surgically treated for thyroid carcinoma (TC) during an 18-year period. Sixty-five of these had papillary, 20 follicular, four medullary and one anaplastic carcinoma. Seventy-eight patients were operated for cure, among these 23 by total thyroidectomy and 55 by partial thyroidectomy. Additional therapy with thyroxine was given to all patients postoperatively. None of the patients treated for cure had died from TC at follow-up 2 to 20 years after diagnosis. One of 42 patients (2.4%) primarily treated for cure with lobectomy for papillary cancer had a local recurrence in the thyroid bed which was excised successfully. No patient treated for cure for follicular cancer had local recurrence. All verified recurrences except one were diagnosed within five years.

It is concluded, that local recurrence after procedures less than total thyroidectomy considered to be curative are unusual provided that thyroxine is given postoperatively. Thus it seems that the reported high rate of microscopic carcinoma in the contralateral lobe in cases with unilateral cancer have little clinical significance. A conservative approach in most cases of localized TC is considered indicated, thus reducing the risk of postoperative complications.

Introduction

The extent of the surgical procedure in the treatment of thyroid carcinoma (TC) is a controversial matter, mainly due to the lack of randomized trials. In particular, there is disagreement whether cancer, clinically confined to one thyroid lobe, should be treated by total thyroidectomy or by more conservative procedures (1-7). Patient materials, not population based, may vary considerably as to distribution of tumor type, stage of the tumor (8,9) and age- and sex composition (10,11). Since these qualities are likely to affect the prognosis in TC, it is difficult to evaluate results of different surgical treatments.

The aim of the present investigation was to evaluate the results of surgical therapy in patients from a demographically well-defined area during the period 1960 to 1977. Particular attention was directed towards the influence of the extent of the thyroid operations on the prognosis.

Material and Methods

The average population in Malmö was 243,000 during the investigated period. The age- and sex distribution was very close to the figures for the Swedish population in 1970.

All treatment and follow-up of TC in patients living in Malmö was taken care of at one hospital. The surgery was almost exclusively carried out by senior surgeons with special interest in thyroid diseases. Until 1971 the surgical treatment could be considered conservative. The strategy was to remove the tumorous thyroid lobe and pathological nodes, while a macroscopically normal contralateral lobe was not touched. During the 1970s, total thyroidectomy became the main procedure and less radical operations were mostly confined to occult cancer incidentally discovered.

In all cases, primarily diagnosed as TC, the histopathological material was

reviewed. Data on surgical procedures and postoperative complications were collected retrospectively from hospital records.

A new TC diagnosis, based on surgical specimens, was made in 120 individuals residing in Malmö during the years 1960 to 1977. Twenty-three of these were excluded because, after histopathological review, the changes were considered benign. Seven patients in whom the only surgical intervention was a biopsy were also excluded, leaving 90 surgically treated patients for evaluation. The age- and sex distribution is shown in figure 1.

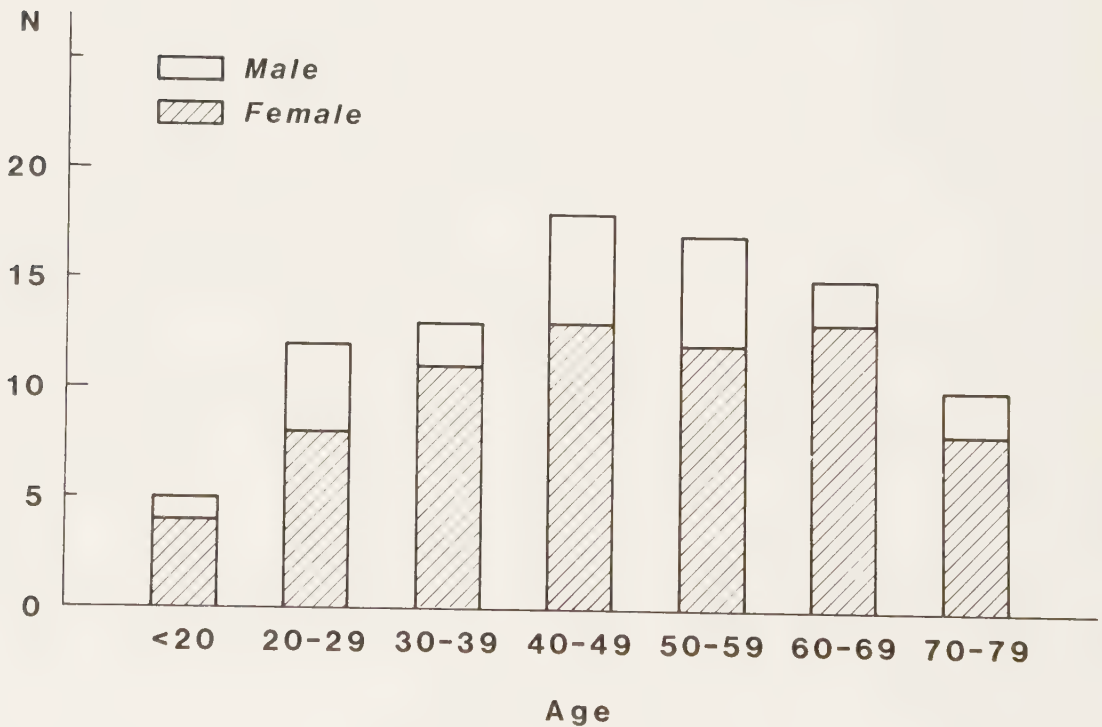


Fig 1: Age and sex distribution in 90 patients surgically treated for thyroid carcinoma.

SURGICAL PROCEDURES

Total thyroidectomy was defined as an operation where all thyroid tissue was removed. When the diagnosis of TC could not be established pre- or peroperatively, the operation was performed in two stages with an interval of one to two weeks. Lobectomy was defined as a procedure where one thyroid lobe, including isthmus, was completely excised. The operation was considered curative when the surgeon peroperatively estimated that all cancer tissue was removed, otherwise the procedure was palliative. During later years the completeness of the total thyroidectomies was checked by thyroid scan, using ^{131}I three to four weeks postoperatively. On the same occasion a "whole-body scan", using the same isotope, was performed to trace distant metastases. Whenever a significant iodine uptake (more than 2% of the supplied dose) was found in the explored region, an ablative dose of ^{131}I was given.

The type of surgical procedure is shown in table I.

Table I: Surgical procedures in 90 patients with thyroid carcinoma.

	Total thyroidectomy n = 30	Lobectomy n = 47	Resections ¹⁾ n = 13
Palliative treatment	4	5	3
Curative treatment	26	42	10
Excision of node metastases	8	16	0
¹⁾ Bilateral n = 6 Unilateral n = 7			

Eight of the 30 total thyroidectomies were performed before 1972, whereas 34 of the 47 lobectomies were performed during the same period of time. Eleven patients, having a lobectomy with partial resection of the opposite lobe, were included among the patients having a lobectomy only. The opera-

tion was considered palliative in twelve cases, in four because of distant metastases, in eight because of inextirpable local growth or regional metastases. "Whole-body scan" was performed in 21 of the 30 patients having a total thyroidectomy.

ADDITIONAL THERAPY

All patients were postoperatively given thyroxine in a dose of 0.1 to 0.3 mg per day. During the later part of the study the completeness of the T_4 -suppression was checked by TRH-test. External radiation therapy was given to five patients surgically treated for palliation and to four treated for cure. Radioiodine treatment for metastases was given to seven and cytostatic drugs to two patients during the follow-up period.

HISTOPATHOLOGY

Histopathological classification was made according to WHO 1974 (12). Only malignant epithelial tumors were included in the study. Occult cancer was defined as a tumor not more than 1.5 cm in its largest diameter, intra-thyroidal cancer as a tumor larger than 1.5 cm not breaking through the thyroid capsule and extrathyroidal cancer as a tumor larger than 1.5 cm with penetration of the thyroid capsule. The definitions of occult, intra-thyroidal and extrathyroidal cancers only apply to the primary tumor without regard to whether or not metastases were present.

Sixty-five patients (72%) had papillary cancer, 20 (22%) follicular, four medullary and one anaplastic. The four medullary tumors were all solitary and apparently non-familial.

The relation between tumor stage and surgical procedure for papillary and follicular cancer is shown in table II. Microscopic growth in the opposite lobe was found in three of 17 patients (18%) treated by total thyroidectomy for clinically one-sided papillary cancer. Three medullary carcinomas were treated with total thyroidectomy while one occult medullary carcinoma was an incidental finding at a thyroid resection for thyrotoxicosis. The patient

SURGICAL PROCEDURE	OCCULT		INTRATHYROIDAL		EXTRATHYROIDAL		N
	Papillary Follicular N=23	N=2	Papillary Follicular N=23	Follicular N=13	Papillary Follicular N=19	Follicular N=5	
Total thyroid- ectomy	6	2	8	4	4	3	18 9
Lobectomy	11	0	12	9	13	1	36 10
Resections	6	0	3	0	2	1	11 1

Table II: Tumor stage and type of surgical procedure in 65 patients with papillary and 20 patients with follicular cancer.

with anaplastic TC had a palliative lobectomy.

FOLLOW-UP

The patients were followed to the closing date of the study, December 31, 1979. Patients followed personally all had a clinical examination, chest X-ray and laboratory screening. Patients examined elsewhere generally had a clinical examination with a laboratory screening once or twice a year and chest X-ray once a year or every two years depending on the time interval from the diagnosis.

Results

At the follow-up all patients except one could be traced. This patient could be followed for four years only. She was included in the study as a four-year control. Twenty patients had died; autopsy was performed in 18 of these. Of the living patients, 38 were examined by one of us, whereas clinical information about 32 patients was collected by review of hospital records or by inquiry to the physician responsible for the TC check-up. The median follow-up time for the 70 patients alive at follow-up was eight years. Fifty-five patients (79%) were followed for five years or more.

PATIENTS TREATED FOR CURE

In 78 patients the surgical procedure was considered to be for cure. Fifty-nine of these had papillary cancer, 15 follicular and four medullary. Sixty-four were still alive at the follow-up, four of them with recurrence (table III)(lung metastases indicated by chest X-ray). In two cases of follicular carcinoma ¹³¹I uptake in the metastases confirmed the X-ray diagnosis. In one patient with papillary cancer a slow radiological progress supported the suspicion of metastases. In the fourth patient with recurrence (papillary), the metastasis was uncertain since the suspected one-centimeter spot on chest X-ray had been unchanged for nine years without treatment.

At follow-up one of the patients with follicular cancer had a clinically advanced disease five years after diagnosis, while the other three patients were considered to have a good quality of life seven, eight and 19 years after diagnosis.

Table III: Results at follow-up, 31 December, 1979, in 90 patients surgically treated for thyroid carcinoma.

	No recurrence		Recurrence or residual TC		Death in TC
	Alive	Dead ¹⁾	Alive	Dead ²⁾	
	n = 61	n = 11	n = 9	n = 5	n = 4
Operation for cure n = 78	60	11	4	3	0
Operation for palliation n = 12	1	0	5	2	4

1) Two patients not autopsied

2) TC at autopsy. TC not main cause of death

Fourteen patients had died at follow-up, eleven without and three with recurrence verified at autopsy (table III). One of the patients with recurrence died from cerebral stroke, but he had lung metastases, suggested *intra vitam* and confirmed at autopsy, to such an extent that it might have been contributory cause of death. Two patients had at autopsy microscopic local residual TC which was considered irrelevant to the death; one of these died postoperatively, the other died from breast cancer metastases.

None of the four patients with medullary carcinoma had recurrence at follow-up.

The different types of recurrence are in table IV related to the extent of the primary surgical procedure.

Table IV: Recurrence in 74 patients with papillary or follicular cancer considered to be operated for cure at the primary surgical procedure.

Type of recurrence	Papillary n=59		Follicular n=15	
	Ttx ¹⁾ n=17	Ptx ²⁾ n=42	Ttx ¹⁾ n=6	Ptx ²⁾ n=9
Clinical recurrence in thyroid gland (surgically treated)	0	1	0	0
Node metastases (surgically treated)	2	2	1	2
Clinically diagnosed distant metastases	1	1 ³⁾	2	1 ⁴⁾
Incidental autopsy finding without clinical significance	0	2	0	0

1) Total thyroidectomy

2) Partial thyroidectomy

3) The recurrence uncertain

4) Dead with recurrence. TC not main cause of death.

Seven patients were surgically treated for node metastases within four years from the primary surgical procedure. One woman, treated by lobectomy for papillary TC at the age of 15, was surgically treated for recurrence at the site of the thyroid gland eleven years later. This patient was still alive without recurrence eight years after the second operation. In four of the five patients with distant metastases at the follow-up, the first sign of recurrence appeared within five years from the primary operation; in the

fifth patient, in whom the recurrence was uncertain, a spot in the right lung was discovered after nine years. The median observation time for the group of patients treated with total thyroidectomy was five years, for the group treated with partial thyroidectomy twelve years. In the latter group, 46 patients (90%) were observed five years or more.

PATIENTS TREATED FOR PALLIATION

In twelve patients the surgical treatment was considered palliative (table I). Six had papillary cancer, five follicular and one anaplastic. The outcome for these patients is shown in table III. The four patients, in whom TC was the main cause of death, had inextirpable local growth (three) or regional metastases (one) at the primary operation.

COMPLICATIONS TO SURGERY

Postoperatively two patients, 63 and 79 years old, died because of pulmonary embolism. Postoperative haemorrhage demanding reoperation occurred in two cases. Vocal cord function could be followed up satisfactorily in 83 patients. Two patients had a preoperative recurrent laryngeal nerve paralysis while in eight cases the nerve was sacrificed deliberately. Of the remaining 73 patients, three had a persistent non-intentional paralysis of one recurrent nerve more than three months postoperatively corresponding to 2.9% of operated thyroid lobes.

One patient, totally thyroidectomized for papillary cancer, had persistent hypocalcemia demanding treatment with vitamin D for more than six months postoperatively, which corresponds to 2.1% of the patients bilaterally operated.

Discussion

In the present study all cases of surgically treated TC from a certain period of time and from a demographically well defined area were studied. Thus, there was no selection of cases, which is a problem in most other studies. Moreover, the histopathological material was reviewed and the diagnoses reclassified to a uniform system. Altogether 90 cases of clinically significant TC were surgically treated during the period of investigation. Epidemiologic and clinical aspects and evaluation of factors (other than surgical) bearing on the prognosis are reported elsewhere (13).

The surgical procedures were classified as total or partial thyroidectomy (table IV). A minor part of the partial thyroidectomies were thyroid resections, mainly performed in patients with occult TC, incidentally discovered (table II) or in patients treated for palliation (table I). Eleven patients, in whom a lobectomy and a resection of the opposite lobe was performed, were included among the patients treated with lobectomy. This could mean an underestimation of the recurrence rate in patients treated for papillary cancer since part of a lobe with possible microscopic cancer foci was removed. None such foci were, however, unveiled at the histopathological examination of the eleven resected, grossly normal thyroid lobes.

It has been maintained that follow-up periods of 15 to 25 years are necessary since deaths caused by TC may occur decades after treatment (5, 14). In the present study none died from TC later than six years after treatment. The verified recurrences appeared during the first five years of observation except in one case. Five of the 20 deaths were proven to be caused by metastases from neoplasms other than TC. From other studies it is generally not stated to what extent autopsy has been performed to confirm TC as cause of death (5,14). The recurrence rate for the patients followed less than five years in the present study might obviously be an underestimation of the true rate. The results concerning patients treated by partial thyroidectomy are, however, considered more reliable than the results for patients treated with total thyroidectomy since the follow-up time in the former group of patients was the longest.

One argument for total thyroidectomy in papillary cancer has been the reported high rate of microscopic cancer foci in the opposite lobe in cases with clinically unilateral tumor (1-3). The frequency of such foci has been reported to be approximately 30% in routine histopathologic examinations (15). More careful histopathological examinations have revealed an even higher frequency (16). In the present study the corresponding figure was found to be 18% at the routine histopathological examinations, where the non-tumor bearing lobe generally had been cut into half centimeter thick slices. This relatively low frequency might be due to the fact that only one of 17 patients, treated with total thyroidectomy for papillary cancer, had been subjected to irradiation therapy to the neck in childhood; such treatment has been suggested to lead to an increased frequency of bilateral involvement (17,18). Clinical recurrence in the opposite thyroid lobe in patients treated with lobectomy for grossly unilateral papillary TC, ought to be a reasonable measure of the significance of microscopic foci in the opposite lobe. However, the reported rates of such recurrences after lobectomy show great discrepancies. Thus, Rose et al report 24.4% recurrence (19), Buckwalter et al 6.8% (4), and Tollefsen et al 4.6% (6). In the present series 42 patients were surgically treated with partial thyroidectomy for papillary cancer (table IV). Local clinical recurrence occurred in one of these (2.4%). However, in this particular case it was impossible to determine if the recurrence was due to a non-radical primary operation or originated from microscopic foci in the opposite lobe. One explanation for the disagreement with other studies might be the relatively low frequency of microscopic foci found in the present study. Another possible explanation is, that all our patients were treated with suppressive doses of thyroxine, since both clinical (5,7,20) and experimental (21-23) studies indicate that growth of TC is influenced by the thyrotropin level. In studies comparable to the present (4,6,19) no mention is made of thyroxine therapy. It may be concluded that lobectomy in most cases of grossly unilateral papillary TC in patients without a history of irradiation to the neck is a sufficient surgical procedure to obtain local tumor control, provided that a suppressive dose of thyroxine is given after the surgical treatment.

The frequency of microscopic cancer foci in the opposite lobe in patients

with clinically unilateral follicular TC seems to be low. In the present study one of nine patients, totally thyroidectomized for follicular cancer, had bilateral involvement which, however, was known preoperatively. None of the 15 patients treated for cure for follicular cancer had local recurrence and it seems reasonable to conclude, in agreement with for instance Tollefsen et al (24), that a thyroid operation adjusted to the clinical extension of the tumor also for follicular TC is sufficient for local tumor control.

One patient with papillary and three with follicular cancer had distant metastases at the presentation. The papillary tumor was occult, two of the follicular tumors were intrathyroidal and one extrathyroidal. In these cases total thyroidectomy is the method of choice because it facilitates treatment with ^{131}I . All four patients with distant metastases had a total thyroidectomy. The three patients with follicular cancer were treated with ^{131}I and were in good health with residual slowly progressing disease three to nine years after the presentation. The patient with occult papillary cancer presented with paraplegia which was found to be caused by a lumbar vertebral metastasis. This metastasis was surgically excised. After thyroidectomy and ^{131}I -therapy he has been followed for six years during which time he has been free from recurrence and neurologic symptoms.

No previously unknown metastases were revealed by the postoperative whole-body scan which was performed in two thirds of the patients treated with total thyroidectomy. Five patients developed lung metastases during the follow-up period which all were diagnosed by X-ray. Other authors have reported cases where metastases from both papillary and follicular cancer have been detected earlier by whole-body scans than by other methods (25, 26). These findings could be one argument for total thyroidectomy if earlier diagnosis of distant metastases means improved survival or quality of life.

The most important argument against total thyroidectomy is the risk of hypoparathyroidism, which is a troublesome complication causing lifelong follow-up and medication. Frequencies of this complication reported in literature vary between three and 27 per cent (15,27,28). It has been

suggested that the risk of hypoparathyroidism can be diminished through a careful surgical technique (27) and through implantation of parathyroid tissue devascularized during the thyroid operation (29). However, the safest way of maintaining normal parathyroid function should be to leave at least two of the parathyroid glands together with adjacent thyroid tissue as in a unilateral procedure. In the present study one patient was considered to have hypoparathyroidism corresponding to 2.1% of the patients at risk and 1.1% of all patients surgically treated for TC.

Another serious disadvantage of total thyroidectomy is the risk of permanent bilateral recurrent laryngeal nerve paralysis causing air-way obstruction. According to reports of complications at total thyroidectomy, this complication seems to be unusual (27,30,31), but through a personal appeal to three laryngologists in Britain, Ridell found 55 such cases (32). In the present investigation no bilateral paralysis occurred in the 30 patients totally thyroidectomized. Our figure of 2.9% for non-intentional unilateral paralysis is satisfactorily low compared to other series (33,34), even though such rates are difficult to compare for methodological reasons. Several patients regained normal vocal cord function during the observation time of three months after a primary postoperative paralysis. The risk of recurrent nerve damage in thyroid surgery has been shown to increase in patients who have a second operation (34). If the primary surgical procedure for TC always is at least a total lobectomy, the risks of postoperative complications at any second operation should not exceed the risk in the primary operation because the tissue close to the nerve and to the parathyroids on the opposite side is unexplored.

CONCLUSIONS

Total thyroidectomy is the method of choice in the treatment of differentiated thyroid carcinoma when the tumor involves the whole gland or when treatment with radioiodine is planned due to distant metastases or non-resectable regional metastases. In other situations the extent of the surgical procedure may be discussed. The high frequency of microscopic foci of papillary cancer in the opposite lobe in cases with grossly

unilateral cancer does not seem to involve an impending risk of clinical recurrence in patients treated with lobectomy. The occurrence of microscopic cancer foci in grossly normal thyroid tissue in follicular cancer is infrequent. Therefore, in most cases of papillary and follicular cancer without distant metastases it should be sufficient to adjust the surgical procedure to the extent of the tumor provided that thyroxine is given in a TSH-suppressive dose postoperatively. The thyroid operation should, however, not be less than lobectomy for the reasons given above.

Acknowledgements

We are deeply indebted to Kaj Lundgren, M.D., at the ENT-department for allowing us to include in the study 16 patients surgically treated at his department. Peter Kitzing, M.D., at the ENT-department has kindly provided us with results of the postoperative laryngoscopy follow-ups.

References

1. Clark RL, Ibanez ML, White EC. What constitutes an adequate operation for carcinoma of the thyroid? *Arch Surg* 1966; 92:23-26.
2. Block MA. Management of carcinoma of the thryoid. *Ann Surg* 1977; 185: 133-144.
3. Sörheide O, Varhaug JE, Heiman P. Thyroid carcinoma: Diagnosis and treatment in 106 patients. *Acta Chir Scand* 1979; 145:137-141.
4. Buckwalter JA, Thomas CG. Selection of surgical treatment for well differentiated thyroid carcinomas. *Ann Surg* 1972; 176:565-577.
5. Cady B. Surgery of thyroid cancer. *World J Surg* 1981; 5:3-14.
6. Tollefsen HR, Shah JP, Huvos AG. Papillary carcinoma of the thyroid. Recurrence in the thyroid gland after initial surgical treatment. *Am J Surg* 1972; 124:468-472.
7. Crile G. Changing end results in patients with papillary carcinoma of the thyroid. *Surg Gynecol Obstet* 1971; 132:460-468.
8. Staunton MD, Skeet RG. Thyroid cancer: Prognosis in 469 patients. *Br J Surg* 1979; 66:643-647.
9. Fraumeni CM, Patchefsky AS, Cobanoglu A. Thyroid carcinoma. A clinical and pathological study of 125 cases. *Cancer* 1979; 43:2414-2421.
10. Mazzaferri EL, Young RL, Oertel JE, Kemmerer WT, Page CP. Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine* 1977; 56:171-196.
11. Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR, Jr. Classification and prognosis of thyroid carcinoma. A study of 885 cases observed in a thirty year period. *Am J Surg* 1961; 102:354-387.
12. Hedinger Chr, Sobin LH, et al. Histological typing of thyroid tumours. International histological classification of tumours, No. 11. Geneva: WHO, 1974:17-24.
13. Borup Christensen S, Ljungberg O, Tibblin S. Thyroid carcinoma in Malmö 1960-1977. Epidemiological, clinical and prognostic findings in a defined urban population. *Cancer*, in press.
14. Tollefsen HR, DeCosse JJ, Hutter RVP. Papillary carcinoma of the thyroid. A clinical and pathological study of 70 fatal cases. *Cancer* 1964; 17: 1035-1044.

15. Clark RL, White EC, Russel WO. Total thyroidectomy for cancer of the thyroid: Significance of intraglandular dissemination. *Ann Surg* 1959; 149:858-866.
16. Russel WO, Ibanez ML, Clark RL, White EC. Thyroid carcinoma. Classification, intraglandular dissemination, and clinicopathological study based upon whole organ sections of 80 glands. *Cancer* 1963; 16:1425-1460.
17. Refetoff S, Harrison J, Karanfilski BT, Kaplan EL, DeGroot LJ, Bekerman C. Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. *N Engl J Med* 1975; 292:171-175.
18. Greenspan FS. Radiation exposure and thyroid cancer. *JAMA* 1977; 237: 2089-2091.
19. Rose RG, Kelsey MP, Russel WO, Ibanez ML, White EC, LeeClark R. Follow-up study of thyroid cancer treated by unilateral lobectomy. *Am J Surg* 1963; 106:494-500.
20. Balme HW. Metastatic carcinoma of the thyroid successfully treated with thyroxine. *Lancet* 1954; 1:812-813.
21. Purves HD, Griesbach WE, Kennedy TH. Studies in experimental goitre; malignant change in transplantable rat thyroid tumour. *Br J Cancer* 1951; 5:301-310.
22. Bielschowsky F. Neoplasia and internal environment. *Br J Cancer* 1955; 9: 80-116.
23. Doniach I, Williams ED. The development of thyroid and pituitary tumours in the rat two years after partial thyroidectomy. *Br J Cancer* 1962; 16: 222-231.
24. Tollefsen HR, Shah JP, Huvos AG. Follicular carcinoma of the thyroid. *Am J Surg* 1973; 126:523-528.
25. Bonte FJ, McConnel RW. Pulmonary metastases from differentiated thyroid carcinoma demonstrated only by nuclear imaging. *Radiology* 1973; 107: 585-590.
26. Casara D, Zorat PL, Busnardo B, Girelli ME. Pulmonary metastases from differentiated thyroid carcinoma detected only by radionuclide imaging. *Br J Radiol* 1981; 54:362-363.
27. Attie JN, Moskowitz GW, Margouleff D, Levy LM. Feasibility of total thyroidectomy in the treatment of thyroid carcinoma. Postoperative radioactive iodine evaluation of 140 cases. *Am J Surg* 1979; 138:555-560.

28. McKenzie AD. The natural history of thyroid cancer. A report of 102 cases analyzed 10 to 15 years after diagnosis. *Arch Surg* 1971; 102:274-277.
29. Salander HE, Tisell LE. Incidence of hypoparathyroidism after radical surgery for thyroid carcinoma and autotransplantation of parathyroid glands. *Am J Surg* 1977; 134:358-362.
30. Katz AD, Bronson D. Total thyroidectomy. The indications and results of 630 cases. *Am J Surg* 1978; 136:450-454.
31. Clark OH. Total thyroidectomy. The treatment of choice for patients with differentiated thyroid cancer. *Ann Surg* 1982; 196:361-370.
32. Riddell V. Thyroidectomy: Prevention of bilateral recurrent nerve palsy. Results of identification of the nerve over 23 consecutive years (1946-69) with a description of an additional safety measure. *Br J Surg* 1970; 57:1-11.
33. Holt GR, McMurtry GT, Joseph DJ. Recurrent laryngeal nerve injury following thyroid operations. *Surg Gynecol Obstet* 1977; 144:567-570.
34. Thompson N, Harness JK. Complications of total thyroidectomy for carcinoma. *Surg Gynecol Obstet* 1970; 131:861-868.

V

Mortality from thyroid carcinoma in a defined population 1960 - 1977.

A clinical and pathological study
of 38 fatal cases

S Borup Christensen and O Ljungberg

Abstract

Thirty-eight cases of fatal thyroid carcinoma (TC) occurred in a demographically well-defined area of, on an average, 243,000 inhabitants during an 18-year period, corresponding to an annual mortality rate of 0.9 per 100,000. The mortality rate did not change significantly during the period of investigation. All diagnoses were based on autopsy findings and were revised histologically. Ten cases were found to have papillary cancer, ten follicular, four medullary and 14 anaplastic. The survival time ranged between 0 and 27 years; two patients with medullary cancer died later than ten years after diagnosis; none of the remaining patients died from the malignant disease later than nine years after TC diagnosis. Nine of the anaplastic tumors contained elements of differentiated TC and five patients who died from anaplastic cancer had had a history of goiter for more than two years. Insufficient surgical treatment (procedures less than lobectomy) was considered partially responsible for the fatal outcome in three of 14 surgically treated patients. Five deaths could be ascribed to complications to treatment. Two patients died postoperatively, two died from late effects of irradiation therapy and one died in a coma caused by insufficient replacement therapy. The TC diagnosis was a *post mortem* surprise finding in ten cases.

Introduction

Mortality rates from thyroid carcinoma (TC) range from 0.2 to 1.3 according to official statistics (1,2). The mortality varies substantially with the different histological types of TC. Thus, anaplastic carcinoma is almost invariably a rapidly killing disease, while the differentiated forms of TC have a good prognosis. Both clinical (3) and mortality (4-6) studies concerning TC have shown that the survival time in fatal cases of differentiated TC often is 10 to 25 years. Accordingly, follow-up times of clinical materials of corresponding length have been recommended. The proportion of late deaths from TC can, however, not be correctly estimated from most previous studies because the patient materials have been selected in various ways and because the causes of death have been incompletely documented.

The present study includes all known deaths from TC during an 18-year period in a demographically well-defined area. The purpose of the study was to determine the true mortality rate in TC, and the survival time for patients with different histological types of TC. An evaluation of to what extent the deaths could be assigned to insufficient treatment or complications to treatment was also made.

Material and Methods

Malmö is a coastal city, situated in an area of the southern part of Sweden where goiter is not endemic (7). During the period of investigation the average population was 243,000. During the years 1960 to 1977 altogether 44,020 individuals died in Malmö. Clinical autopsy was performed in 68% of these and in approximately 95% of the patients who died in hospital. (Medico-legal autopsy was performed in a further 18% of the individuals who died in Malmö.) The clinical autopsies were performed in a standardized way and included examination of the thyroid gland. The gland was cut into slices about half a centimeter thick or less. All slices were carefully inspected and whenever a lesion was detected which arose suspicion of

tumor, a supplementary histologic examination was made.

Diagnoses of TC were searched for in the registry at the Department of Pathology where all autopsy diagnoses, made at the clinical autopsies, are recorded. Altogether 114 cases of TC were found. In 49, TC was considered main or contributory cause of death, whereas in 65 cases it was considered to be a finding without relevance to the death. Eleven of the 49 cases were excluded from the study because, after histopathological review, the malignant disease in these cases was considered secondary to non-thyroidal malignant tumors. The remaining 38 cases form the basis for the present study. Information from the National Cancer Registry on diagnoses of TC in Malmö, was available from 1958 through 1974. A review, however, unveiled no further cases of deaths from TC.

The histopathologic classification was made according to WHO in 1974 (8). Only malignant epithelial tumors were included.

Patient history, clinical manifestations and therapy were studied retrospectively from hospital records. All available surgical specimens from previously performed thyroid operations were reexamined and reclassified.

DEFINITIONS

Survival time: The time interval from the histologic, cytologic and/or clinical diagnosis to death. Age-specific mortality rate: The average annual number of deaths from TC in each 10-year age-group per 100,000 of the average population in that age-group. Age-standardized mortality rate (hereafter called mortality rate): The average annual crude mortality rate per 100,000 persons adjusted for age to the Swedish population in 1970.

Results

The average mortality rate was 0.9. During three six-year periods (1960-1965, 1966-1971, and 1972-1977) the mortality rates were 1.3, 0.7, and 0.8, respectively. The difference between the rates was not significant (9). The age and sex distribution and the age specific mortality rates appear from figure 1. The ratio between men and women was 1:1.4, the age range at death

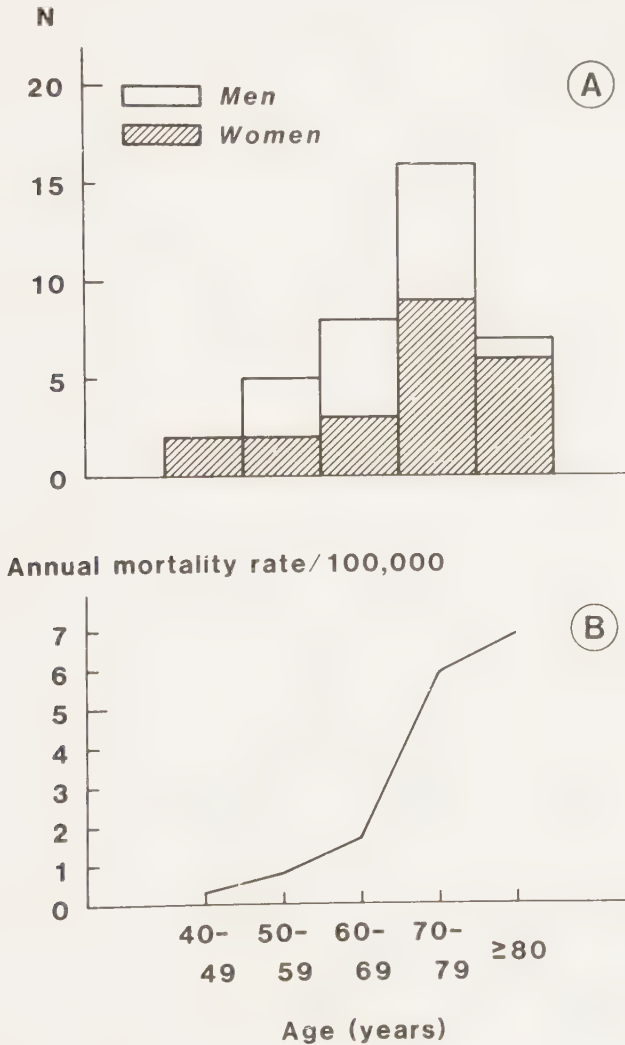


Fig 1: Age and sex distribution (A) and age specific mortality rate (B) in 38 cases of fatal TC.

41 to 90 years. The age-specific incidence (age at diagnosis) for the cases in the present study, contrasted to the age-specific incidence of all clinical TC during the same period of time (10) is given in figure 2. It seems that relatively few patients with a diagnosis of TC before the age of 60 die from the disease, whereas TC diagnosed after this age increasingly often is fatal.

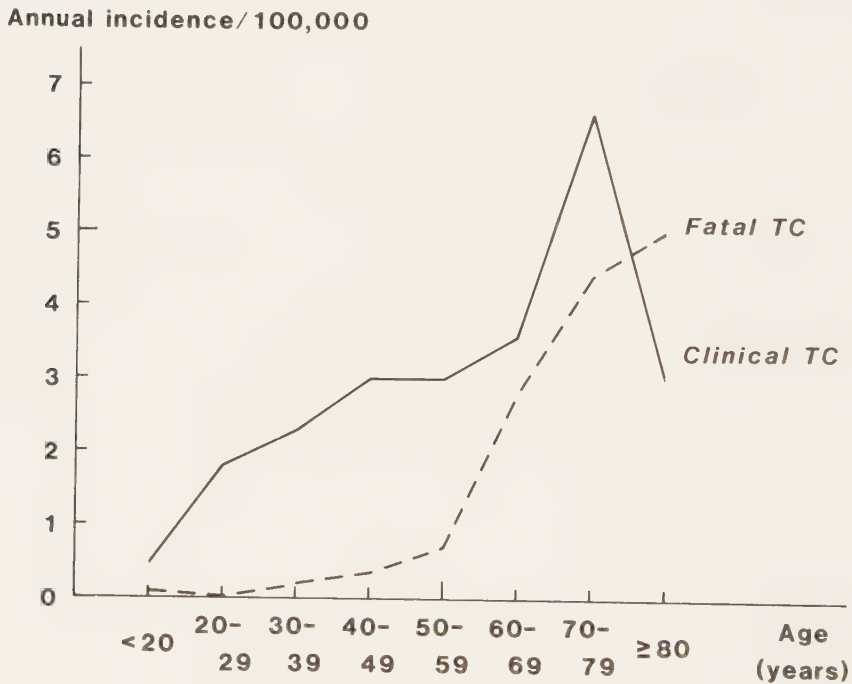


Fig 2: Age specific incidence (age at diagnosis) in 104 patients with clinical TC, and in 38 patients in whom the TC was fatal.

In 27 cases the death was directly caused by the tumor and/or its metastases. In six cases another disease was recorded as the main cause of death, although metastases from TC were considered strongly to contribute to the death. In five cases the death could be ascribed to complications of treatment for TC.

The histopathologic findings are presented in table I. Three of the five

Table I: Tumor distribution at autopsy in 38 patients deceased from TC related to histologic type.

Histologic type	Tumor extension			
	Local growth	Regional metastases	Distant metastases	No TC *
	n = 31	n = 21	n = 31	n = 3
Papillary n = 10	6	6	6	1
Follicular n = 10	8	2	8	2
Medullary n = 4	3	3	4	0
Anaplastic n = 14	14	10	13	0

* Death caused by treatment for TC

patients who died from complications to treatment had no residual TC at autopsy. Local growth causing mechanical obstruction of vital structures in the neck was considered the cause of death in two cases of papillary carcinoma and in three cases of anaplastic carcinoma. In the remaining 28 cases the disseminated malignant disease was the cause of death. All 14 anaplastic carcinomas were of the giant cell type. Nine of the anaplastic tumors also contained elements of differentiated TC; five of these were of follicular type and four were papillary. The most common locations of distant metastases are shown in table II.

Table II: Location of distant metastases at autopsy in patients deceased from TC by histological type.

Histologic type	Lung n=24	Bone n=16	Liver n=11	Pleura n=9	Other n=15
Papillary n = 10	6	1	1	0	1
Follicular n = 10	5	7	2	1	5
Medullary n = 4	3	2	3	2	1
Anaplastic n = 14	10	6	5	6	8

The mean ages at diagnosis and at death (figures within brackets) in cases with the different tumor types were: papillary 63 years (69), follicular 69 years (71), medullary 48 years (58), anaplastic 74 years (74).

CLINICAL COURSE

Papillary cancer

Eight of the ten papillary carcinomas were histologically verified *intra vitam*, one was suggested clinically, and one was a *post mortem* surprise finding (table III). The survival time ranged between 0 and 20 years for the nine patients with a clinical diagnosis of TC (table IV). Two patients died postoperatively from pulmonary embolism. One 35-year-old woman died 20 years after the presentation from pulmonary fibrosis. This was considered to be caused by irradiation therapy given for suspected mediastinal node metastases one year after the primary operation. At autopsy she had minimal residual TC considered irrelevant as cause of death. The survival time

Table III: The basis for TC diagnosis in 38 patients deceased from TC related to histologic type.

Histologic type	Basis for diagnosis			
	Histologic examination of surgical specimen n = 19	Fine-needle aspiration biopsy n = 4	Clinical examination n = 5	Autopsy * n = 10
Papillary n = 10	8	0	1	1
Follicular n = 10	5	0	0	5
Medullary n = 4	2	0	0	2
Anaplastic n = 14	4	4	4	2

* TC surprise finding post mortem

ranged from one to nine years in the remaining six cases. Seven patients had been subjected to surgical treatment (table V). This was considered to be curative in four; one of these died postoperatively, one died from pulmonary fibrosis and two died from distant metastases. At autopsy, one of the patients treated for cure, had a recurrent tumor in the thyroid region, while the other cases, curatively treated, were free from local recurrence.

Follicular cancer

Five of the ten follicular carcinomas were *post mortem* surprise findings (table III). In two cases there was no clinical suspicion of tumor while in

Table IV: Survival time for 28 patients deceased from TC, where the diagnosis of TC was made in life related to histologic type.

Histologic type	Survival time (years)				
	<1	1 - 5	5 - 10	10 - 20	> 20
Papillary n=9	3	3	2	1 ¹⁾ (20years)	-
Follicular n=5	1	4	-	-	-
Medullary n=2	-	-	-	1 (13years)	1 (27years)
Anaplastic n=12	12	-	-	-	-
Total	16	7	2	2	1

1) Died from complications to treatment

three cases metastases from follicular cancer were clinically suggested to be meningioma, chordoma in the pelvis, and metastases from prostatic carcinoma, respectively. In the five patients with a clinical diagnosis of follicular carcinoma, the survival time ranged from ten months to five years (table IV). Four patients had been treated surgically (table V). In two of them the surgical procedure was considered palliative, in the other two curative. One of the patients treated for cure died five years after diagnosis from pulmonary fibrosis which was interpreted as a sequel of irradiation therapy to the mediastinum given for recurrent node metastases two years after the primary operation. The other patient treated for cure died in a coma, probably caused by insufficient replacement therapy for hypothyroidism and hypoparathyroidism. She had refused to come to follow-up. None of these two patients had recurrent TC at autopsy.

Table V: Treatment of 38 patients deceased from TC

Histologic type	Surgery n = 14	External radiation therapy n = 18	^{131}I n = 7	Cytostatic drugs n = 4	No therapy n = 15
Papillary n = 10	7	4	3	1	2
Follicular n = 10	4	6	2	1	4
Medullary n = 4	2	2	0	0	2
Anaplastic n = 14	1	6	2	2	7

Medullary carcinoma

In two cases from this group the TC diagnosis was a *post mortem* surprise finding (table III). In one of these, metastases from medullary carcinoma had been treated surgically seven years earlier but was then histologically interpreted as ependymoma. In the other case there was no clinical suspicion of tumor. Both cases were considered sporadic since screening of their relatives had not unveiled any further cases of medullary carcinoma.

In two cases the medullary tumor was considered part of a multiple endocrine neoplasia syndrome since both had bilateral pheochromocytoma at autopsy and one also multiple oral and ocular neuromas. Both patients had been surgically treated and the diagnosis of TC was settled at these occasions; the particular medullary type of the TC was, however, not elucidated until autopsy. The patients were 14 and 45 years of age at the cancer diagnosis and survived 27 and 13 years respectively (table IV). One of the patients

had been adopted and her biological family could not be traced. In the other case several family members at later screening were found to have both medullary carcinoma and pheochromocytoma.

Anaplastic cancer

In four of the 14 cases the diagnosis was histopathologically verified *intra vitam* (table III). Four had a cytologic diagnosis of cancer by aspiration biopsy and in four TC was suggested clinically. In two cases the autopsy diagnosis was a surprise finding.

The treatment appears from table V. Only one patient had been subjected to surgical therapy. The survival time was in all 14 cases less than one year (table IV).

In five patients a mass in the neck had been noted two to 36 years before death, and one had been surgically treated for oxyphil cell adenoma twice; histopathologic review of the surgical specimens from these occasions unveiled no malignancy.

Discussion

One of the objectives in the present study was to estimate the true mortality rate of TC in Malmö. Therefore it was important that all cases, where TC directly or indirectly was considered cause of death during the period of investigation were included in the study. All deaths from a TC, diagnosed between 1958 and 1974 should be included in the study, because all cancer diagnoses in Sweden are notifiable to the National Cancer Registry. The majority of those patients with a diagnosis of TC before 1958, who died from TC during the period of investigation, are probably also included because autopsy was performed in 95% of all patients who died in hospital.

The mortality rate from TC in the whole of Sweden was, on an average, 1.3 during the period 1960 to 1977 according to official death statistics (2). The corresponding figure for Malmö found in the present study was 0.9. The causes of death in Malmö are considered more reliable than in the rest of Sweden because 68% of the death certificates in Malmö were based on autopsy records corresponding to 40% in the whole country (disregarding medico-legal autopsies). The difference of 0.4 in mortality rate is probably due to inclusion in the official figures of patients not dying from TC. The number of cases with fatal TC in the present study was reduced with approximately 20% at the histopathological review. So, it is assumed that official figures for mortality rates of TC might be overestimations of true mortality rates.

The age-standardized mortality rate did not change significantly during the period of investigation; also in whole Sweden the mortality rate was rather stable during the same period of time. The incidence of TC, on the contrary, increased steadily with about 22% in Sweden from 1960 to 1977 (11), and in Malmö the incidence of clinical TC increased by about 30% during the 1970s (10). One possible explanation for the difference in trend between mortality rate and incidence might be that more relatively benign tumors were diagnosed during later years because of increased health awareness and availability of medical care.

The importance of age for the prognosis as emphasized by many authors (12-14) is strongly supported in the present study (fig 2). One explanation for the increasing mortality with age is the late onset of anaplastic TC, but also a higher mortality in older than in younger patients with differentiated TC is contributing. Thus, the mean ages at diagnosis for patients with papillary and follicular TC in the present study were considerably higher than the corresponding mean ages for all patients with such tumors in Malmö (10). In the interpretation of figure 2, it is important to take into consideration that autopsy surprise findings of fatal TC (ten cases) were not included in the conception of clinical TC. In fact, this can explain why the incidence of "fatal TC" after the age of 80 exceeds the incidence of "clinical TC".

The survival times in fatal cases of papillary and follicular TC in the present study were relatively short compared to other series (3,4); only one patient died more than ten years after diagnosis (table IV) and in this case the death was not caused by the malignant disease itself but from side effects to treatment for TC. According to a report by Tollefsen et al on fatal cases of papillary TC, 27% of the cases had died more than ten years after diagnosis (4). In this study the causes of death were, however, verified by autopsy in only 11%. Autopsy findings are, of course, always more reliable than clinical judgements as basis for causes of death, but this is particularly true for a slow-growing tumor like differentiated TC, because other malignant tumors have time to develop and set metastases (10,15). However, the discrepancy in proportion of late deaths between the present and other studies can probably not solely be explained by the difference in autopsy documentation. Other factors like selection of cases, difference in the natural history of TC, and difference in treatment may also be of importance.

The ratio between men and women in patient materials of clinical TC usually is reported to be about 1:3 (10,13,16). In the present, and other, studies concerning fatal TC (6,17), the proportion of women is considerably lower than in clinical materials. This discrepancy in sex ratio indicates that the prognosis of TC, clinically diagnosed in women, is better than in men.

One important question is whether the fatal outcome in any of the 14 patients surgically treated could be attributed to insufficient surgical therapy. Seven patients were, according to the surgical report, considered to be surgically treated for cure. At autopsy eight to 27 years after the primary surgery three of these (two with medullary carcinoma, one with papillary carcinoma) had besides distant metastases also local recurrence. In all these three patients the surgical procedure was less than lobectomy. A more extensive primary surgical procedure may have saved the patients from disseminated disease. The remaining four cases surgically treated for cure had had at least a lobectomy. None of these revealed local recurrence at autopsy. It may be concluded that in surgical treatment of local curable TC, a complete lobectomy should be the least procedure recommended.

Five patients (13%) died as a result of the therapy for TC. In both cases of postoperative deaths the surgical procedures were protracted, the patients were above 60 years of age, and the causes of death were pulmonary embolism. Whenever long surgical procedures in elderly are to be expected, some form of thrombo-prophylaxis should come into consideration even in thyroid surgery. Two patients died five and 20 years after the TC diagnosis as a consequence of irradiation therapy to the mediastinum. It is impossible to estimate whether these patients could have managed better without radiologic therapy. One of the patients, however, was a young woman with an occult papillary TC with lymph node metastases. Such cases are reported to have favorable prognosis after surgical therapy alone (18,19). It is therefore considered important to take into account the relatively benign course of differentiated TC when radiation therapy is considered.

The poor prognosis of anaplastic TC reported by others (20-23), irrespective of the treatment given, was confirmed in the present study. All 14 patients with this diagnosis died within one year. Nine of the anaplastic carcinomas contained elements of differentiated TC; in about one third of the cases a goiter had been noted during a varying number of years before the anaplastic carcinoma killed the patient. These findings support earlier suggestions that anaplastic carcinoma may develop from differentiated TC (6,17,20-23), which may have been present for several years. Unfortunately, we do not know how to identify those tumors which are prone to undergo anaplastic transformation.

In ten cases (26%), the TC was a surprise finding *post mortem*. Seen retrospectively, some of these might have been diagnosed *intra vitam*; this is considered important for differentiated TC, even when distant metastases occur, because therapy by total thyroidectomy supplemented by ^{131}I has a good chance to be successful (24).

References

1. Schottenfeld D, Gershman ST. Epidemiology of thyroid cancer. *CA-A Cancer Journal for Clinicians* 1978; 28:66-86.
2. Causes of death 1960-1977. Official statistics of Sweden. National Central Bureau of Statistics. Stockholm, 1960-1977.
3. Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Ramagosa V, Werberg J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. *Ann Surg* 1976; 184:541-553.
4. Tollefsen HR, DeGosse JJ, Hutter RVP. Papillary carcinoma of the thyroid. A clinical and pathological study of 70 fatal cases. *Cancer* 1964; 17: 1035-1044.
5. Konrad HR, Canalis RF. Lethal thyroid carcinoma. *Arch Otolaryngol* 1978; 104:454-455.
6. Silverberg SG, Hutter RVP, Foote FW. Fatal carcinoma of the thyroid: histology, metastases, and causes of death. *Cancer* 1970; 25:792-802.
7. Höjer JA. Kropfstudien. Svenska Läkarselskapets handlingar 1931; 57: 1-104.
8. Hedinger C, Sobin LH et al. Histological typing of thyroid tumours. International histological classification of tumours, No. 11. Geneva: WHO, 1974: 17-24.
9. Cox DR. Some simple approximate tests for Poisson variates. *Biometrika* 1953; 40:354-360.
10. Borup Christensen S, Ljungberg O, Tibblin S. Thyroid carcinoma in Malmö 1960-1977. Epidemiological, clinical and prognostic findings in a defined urban population. *Cancer* (in press).
11. Cancer incidence in Sweden 1977. National Board of Health and Welfare. The Cancer Registry, Stockholm; 1981, p 24.
12. McKenzie AD. The natural history of thyroid cancer. A report of 102 cases analyzed 10 to 15 years after diagnosis. *Arch Surg* 1971; 102:274-277.
13. Beaugié JM, Brown CL, Doniach I, Richardson JE. Primary malignant tumors of the thyroid: the relationship between histological classification and clinical behavior. *Br J Surg* 1976; 63:173-181.
14. Fraumeni CM, Patchefsky AS, Cobanoglu A. Thyroid carcinoma. A clinical and pathological study of 125 cases. *Cancer* 1979; 43:2414-2421.

15. Bondeson L, Bondeson AG, Ljungberg O, Tibblin S. Oxyphile tumors of the thyroid. Follow-up of 42 surgical cases. *Ann Surg* 1981; 194:677-680.
16. Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR. Classification and prognosis of thyroid carcinoma. A study of 885 cases observed in a thirty-year period. *Am J Surg* 1961; 102:354-387.
17. Ibanez ML, Russel WO, Albores-Savedra J, Lampertico P, White EC, LeeClark R. Thyroid carcinoma - biologic behavior and mortality. Post-mortem findings in 42 cases, including 27 in which the disease was fatal. *Cancer* 1966; 19:1039-1052.
18. Woolner LB, Lemmon ML, Beahrs OH, Black BM, Keating FR. Occult papillary carcinoma of the thyroid gland: a study of 140 cases observed in a 30-year period. *J Clin Endocrinol* 1960; 20:89-105.
19. Hubert JP, Kiernan PD, Beahrs OH, McConahey WM, Woolner LB. Occult papillary carcinoma of the thyroid. *Arch Surg* 1980; 115:394-398.
20. Jereb B, Stjernswärd J, Löwhagen T. Anaplastic giant-cell carcinoma of the thyroid. A study of treatment and prognosis. *Cancer* 1975; 35:1293-1295.
21. Aldinger KA, Samaan NA, Ibanez M, Hill CS. Anaplastic carcinoma of the thyroid. A review of 84 cases of spindle and giant cell carcinoma of the thyroid. *Cancer* 1978; 41:2267-2275.
22. Nishiyama RH, Dunn EL, Thompson NW. Anaplastic spindle-cell and giant-cell tumors of the thyroid gland. *Cancer* 1972; 30:113-127.
23. Harada T, Kunihiro I, Shimaoka K, Hosoda Y, Yakumaru K. Fatal thyroid carcinoma. Anaplastic transformation of adenocarcinoma. *Cancer* 1977; 39:2588-2596.
24. Leeper RD. The effects of ¹³¹I therapy on survival of patients with metastatic papillary or follicular thyroid carcinoma. *J Clin Endocrinol Metab* 1973; 36:1143-1152.

